

# **Knee osteoarthritis and knee function after anterior cruciate ligament reconstruction Long term results**

**PhD Thesis**

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## **Errata**

Page 13, line 20: Spelling mistake; corrected from emanate to emanates

Page 25, line 15: Spelling mistake; corrected from paper to Paper

Page 26, Figure 1, Spelling mistake; corrected from paper to Paper

Page 27, Figure 2, column 3: Spelling mistake; corrected from ostoearthirits to osteoarthritis

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## Abbreviations

|         |  |
|---------|--|
| ACL     | Anterior cruciate ligament   |
| ACR     | American College of Rheumatology                                   |
| ADL     | Activities of daily living   |
| AMI     | Arthrogenic muscle inhibition                                      |
| ANOVA   | Analysis of variance   |
| BMI     | Body mass index  |
| BPTB    | Bone-patellar-tendon-bone  |
| CI      | Confidence interval  |
| CMS     | Coleman Methodology Score  |
| CNS     | Central nervous system   |
| CONSORT | Consolidated Standards of Reporting Trials                         |
| HT      | Hamstrings tendon  |
| ICF     | International Classification of Functioning, Disability and Health |
| IKDC    | International Knee Documentation Committee                         |
| J       | Joule  |
| JSN     | Joint space narrowing  |
| JSW     | Joint space width  |
| k       | Kappa  |
| KOOS    | Knee Injury and Osteoarthritis Outcome Score                       |
| K&L     | Kellgren and Lawrence  |
| LCL     | Lateral collateral ligament  |
| MCL     | Medial collateral ligament   |
| MD      | Medical doctor   |
| MRI     | Magnetic resonance imaging   |
| MSc     | Master of Science  |
| NAR     | Norwegian research center for Active Rehabilitation                |
| OA      | Osteoarthritis   |
| OARSI   | Osteoarthritis Research Society International                      |
| OR      | Odds ratio   |
| OSTRC   | Oslo Sports Trauma Research Center                                 |

|           |                                  |
|-----------|----------------------------------|
| PT        | Physical therapist               |
| QOL       | Quality of life                  |
| RCT       | Randomized controlled trial      |
| ROM       | Range of motion                  |
| SD        | Standard deviation               |
| SPORT/REC | Function in sport and recreation |
| TW        | Total work                       |
| VAS       | Visual analogue scale            |
| WHO       | World Health Organization        |
| WOMAC     | Western Ontario and McMaster     |

## **List of Papers**

### **Paper I**

Øiestad BE, Engebretsen L, Storheim K, Risberg MA. Knee Osteoarthritis After Anterior Cruciate Ligament Injury. A Systematic Review. *Am J Sports Med* 37:1434-1443, 2009

### **Paper II**

Øiestad BE, Holm I, Aune AK, Gunderson R, Myklebust G, Engebretsen L, Fosdahl M, Risberg MA. Knee function and prevalence of knee osteoarthritis after anterior cruciate ligament reconstruction. A prospective study with 10-15 years follow-up. Accepted *Am J Sports Med*, April 20, 2010

### **Paper III**

Øiestad BE, Holm I, Engebretsen L, Risberg MA. The association between radiographic knee osteoarthritis and knee symptoms, function, and quality of life 10-15 years after anterior cruciate ligament reconstruction. Accepted *Br J Sports Med*, June 2, 2010

### **Paper IV**

Øiestad BE, Holm I, Myklebust G, Gunderson R, Risberg MA. Quadriceps muscle weakness after anterior cruciate ligament reconstruction: a risk factor for knee osteoarthritis? Accepted *Arthritis Care & Research*, July 7, 2010

## Preface

This PhD thesis is a long term follow-up study of subjects with anterior cruciate ligament (ACL) injury and subsequent ACL reconstruction. The thesis consists of four Papers: one systematic review of long term follow-up studies of ACL injured subjects (Paper I), and three studies on subjects with ACL reconstruction (Paper II-IV). A total of 258 patients were included consecutively in four studies with 2 years follow-up from 1990 to 1997, and they were all tested with identical functional and clinical tests. This PhD thesis is a 10-15 year follow-up of these 258 subjects.

This study was started in 1990 by Physical therapist (PT) May Arna Risberg at Ullevaal University Hospital. She initiated research collaboration with PT Inger Holm at Sophies Minde Orthopaedic Hospital. Fifty-nine patients scheduled for ACL reconstruction at Bærum Hospital were included in a prospective cohort study examining changes in impairments and disabilities after ACL reconstruction. Furthermore, a randomized controlled trial (RCT) was carried out at Ullevaal University Hospital including 60 subjects scheduled for ACL reconstruction. In this study, the effect of knee bracing after ACL reconstruction was examined. While these two studies were ongoing, two RCTs were initiated by Medical doctor (MD) Arne Kristian Aune at Martina Hansens Hospital and at Ullevaal University Hospital. These two RCTs included 67 and 72 patients scheduled for ACL reconstruction, and explored the effects of mini-open versus endoscopic procedure and bone-patellar-tendon-bone (BPTB) graft versus hamstrings tendon (HT), respectively. Professor May Arna Risberg and Professor Inger Holm followed and tested all these subjects in the four prospective studies at 6 months, 1 year, and 2 years postoperatively. In addition, Professor Lars Engebretsen, Radiologist Ragnhild Gunderson, associate Professor Grethe Myklebust, Master of Science (MSc) and PT Merethe Aarsland Fosdahl, and research coordinator MSc Kristin Bølstad have been involved in the 10-15 year follow-up. The Department of Orthopaedics at Ullevaal University Hospital and the Rikshospitalet University Hospital now merged into the new Oslo University Hospital are acknowledged for the support and working facilities provided for this long term follow-up study.

## Introduction

### Anterior cruciate ligament injury

The annual rate of anterior cruciate ligament (ACL) reconstructions in Norway has been reported to be more than 1500, or an annual population incidence of 34/100 000 (data from The Norwegian National Knee Ligament Registry 2006-2009)<sup>70</sup>. The annual rate of ACL injuries in Norway is estimated to about 4000<sup>71</sup>, and about 40% of the individuals that suffer an ACL injury in Norway undergo surgical treatment. The main population at risk is between 16 to 39 years, and the annual incidence for the population at risk has been reported to be 85/100 000<sup>70, 155</sup>. Females have shown a higher risk for suffering ACL injuries than males<sup>5, 16, 150</sup>. The ACL injuries occur mostly during pivoting sport activities such as team handball, soccer, football, basket, or alpine skiing<sup>127, 129, 155</sup>. The injury may occur during contact with another player, but non-contact situations in sports do more often lead to an ACL injury<sup>9, 152, 189, 204</sup>. A typical situation for tearing the ACL is when the knee collapses medially, the so-called valgus collapse, or when the player lands with an external rotation of the tibia in relation to the femur with the knee near full extension<sup>9, 105</sup>. Evidence exists that an injury mechanism also may involve internal rotation of the tibia in relation to the femur<sup>204</sup>. Common for the injury mechanisms are rapid accelerations and high frequency of the movements combined with deceleration and landing or pivoting the knee in near full extension<sup>105, 189</sup>.

The ACL is a double bundled ligament with a length of approximately 30-40 mm<sup>14, 138</sup>. The femoral insertion for the ACL is located at the posterior part of the medial surface of the lateral femoral condyle. The anteromedial bundle emanates from the proximal part of the femoral insertion to the anteromedial part of the tibial insertion, which is located anteriorly and laterally on the medial tibial plateau<sup>55</sup>. The posterolateral bundle comes from the distal part of the femoral insertion, to the posterolateral part of the tibia<sup>55, 94, 185, 216</sup>. The aim of the ACL is primarily to stabilize the tibia from anterior displacement relative to the femur, but the ACL also plays a role in stabilizing the internal or external rotation of the tibia in relation to the femur and the varus-valgus movement<sup>29, 61</sup>. The two bundles have been shown to have different tasks related to the stabilizing process during the knee flexion-extension movement: the anteromedial bundle becomes taut during flexion, and the posterolateral bundle becomes taut during extension<sup>145, 186</sup>.

Treatment procedures for ACL injuries include surgical reconstruction of the ligament with subsequent postoperative rehabilitation, or nonoperative rehabilitation with emphasis on neuromuscular exercises and strength training in order to restore dynamic stability of the knee joint<sup>28, 29</sup>. No clear decision guidelines exist on whether the individual patient should go through surgical treatment or nonoperative rehabilitation. The choice of treatment is in our country usually decided by the patient in counselling with their orthopaedic surgeon on the basis of the patient's knee function and the desired future activity level<sup>29</sup>. Few randomized controlled trials (RCT) exist comparing surgical and nonoperative treatment<sup>113, 125</sup>, however, several retrospective observational studies including subjects who have undergone ACL reconstruction as well as subjects who have followed nonoperative treatment exist<sup>99, 115, 124, 205</sup>. Thus, on the basis of the existing literature we do not have enough evidence to state whether surgical or nonoperative treatment is the most optimal treatment for subjects with ACL injuries. Those who return to pivoting sports may benefit from surgical treatment to prevent episodes of giving way and/or to prevent occurrence of additional injuries to the menisci or cartilage<sup>29, 113, 114</sup>. Repeated episodes of giving way, increased knee joint laxity, and associated injuries to the menisci have been shown to be common indications for surgery<sup>29</sup>.

Through the last decades the reconstruction procedures have changed from open surgery with primary sutures to arthroscopic assisted procedures using autografts or allografts<sup>122</sup>. The advances in surgical procedures have resulted in faster rehabilitation and earlier return to pre-injury level of function<sup>146</sup>. The most common graft type in Norway today is hamstrings tendon (HT) graft followed by bone-patellar-tendon-bone (BPTB) graft<sup>70</sup>. The grafts are usually constructed by tendons from the mid third of the patellar tendon (BPTB) or from the semitendinosus and gracilis tendons (HT)<sup>122</sup>.

There has also been a substantial evolution in rehabilitation programs after ACL injury and surgery. More aggressive function-based pre- and postoperative rehabilitation programs have been introduced and incorporated, replacing the time-based more conservative algorithms from the past. Early quadriceps strength training, and neuromuscular exercises, including both open and closed kinetic exercises are now emphasised in the rehabilitation<sup>73, 142, 157</sup>. There seems to be agreement in the literature that rehabilitation strategies following ACL reconstruction should focus on maximizing knee extensor strength via exercises targeting inhibition and atrophy to restore the

dynamic knee joint stability and range of motion (ROM)<sup>73</sup>. Furthermore, knee-specific exercises targeting return to sport are usually included for those who aim to return to sport<sup>202</sup>. Nevertheless, there is still no consensus in the literature regarding what might constitute the best rehabilitation program for subjects that have undergone ACL reconstruction<sup>73, 202</sup>, although several RCTs and reviews exist<sup>162, 199, 200, 211, 212</sup>.

### **Additional knee injuries after anterior cruciate ligament injury**

ACL injuries are often seen in combination with associated injuries to the menisci or other ligaments, mostly the medial collateral ligament (MCL), the cartilage, or the subchondral bone<sup>114</sup>. About 50-60% of the ACL injuries include additional injuries to the menisci or the cartilage<sup>114, 137</sup>. Lateral meniscal injuries have been shown to be slightly more frequent than medial tears in the acute injury situation<sup>93, 186</sup>, while medial meniscal injuries are more frequent in chronic ACL deficiency<sup>155</sup>. There is evidence that the risk of additional medial meniscus injuries increases with time from injury to reconstruction<sup>114, 137</sup>. However, it is not clear if this is due to type or level of activity<sup>137</sup>. As the lateral meniscus carries higher loads than the medial meniscus, worse outcome has been shown after lateral meniscectomy<sup>57</sup>. The risk of additional injury to the menisci has been shown to be higher for males than for females<sup>137</sup>. The meniscal injuries may be symptomatic or asymptomatic and may not be associated with loss of mechanical stability<sup>57</sup>. Englund<sup>57</sup> has briefly summarized the historical view of treatment methods of meniscal tears, which started with sutures in 1883 followed by total meniscectomy only four years later that lasted for a century. From about 1970 a growing interest appeared regarding the biomechanical changes that occurred in the knee joint after total meniscectomy. As a result of several biomechanical studies on the menisci, sutures became again a treatment alternative in addition to partial meniscectomy.

Chondral lesions are also commonly associated with ACL injuries, and have been detected in between 11% to 43% of acute ACL injuries<sup>70, 137</sup>. Chondral lesions are often graded after the Outerbridge system (grade 0-4) where grade 0 is normal cartilage, and 4 is deep chondral lesion >2mm in diameter and down to subchondral bone<sup>44, 140</sup>. Treatment methods have been developed to reduce symptoms, increase function, and to restore biomechanical conditions in the knee joint. Surgical techniques include lavage, debridement, drilling techniques to stimulate tissue growth, microfracture, osteochondral autograft transplantation, and autologous chondrocyte implantation<sup>23</sup>.

<sup>116, 154</sup>. Bone bruises are demonstrated in the majority of subjects with ACL injuries<sup>62, 204</sup>, but no long term consequences of bone bruises have been reported<sup>80</sup>.

MCL injuries are reported in approximately 5% of subjects with ACL injury, while lateral collateral ligament injuries (LCL) in combination with ACL injury are rare (1%)<sup>70</sup>. The MCL has been found to heal spontaneously and the ACL has shown to compensate for part of the functional deficits in valgus rotation when the MCL is torn<sup>94</sup>. Treatment strategies for a torn MCL (grade III) involve conservative treatment with a brace or surgical repair<sup>45, 207</sup>.

### **Knee function after anterior cruciate ligament injury and reconstruction**

The concept of knee function is not easily defined, and thus, a wide set of valid assessment tools may be used to cover the measurement of knee function. Knee function can be defined according to the International Classification of Functioning, Disability and health (ICF) developed by the World Health Organization (WHO). According to this classification knee function may include aspects concerning both body structures and function and aspects concerning activity and participation<sup>209</sup>. Impaired knee function in subjects with ACL reconstruction may involve loss of normal physiological functioning of body structures or systems such as muscle weakness and pain, but it may also involve activity limitations in pivoting sports or activities of daily living<sup>118</sup>.

An ACL rupture often leads to dynamic knee joint instability<sup>169</sup>. The dynamic knee joint stability can be defined as the stability of the knee joint through rapid changes in position and is dependent on both ligaments, menisci, muscles, and other tissues surrounding the knee joint<sup>26</sup>. The ACL contains sensory structures which give feedback to the central nervous system (CNS) which furthermore provides adequate activation of the structures that ensure dynamic knee joint stability<sup>192</sup>, for instance quadriceps and hamstrings muscle strength. This pathway may be disturbed after an ACL rupture. Dynamic knee joint instability after an ACL rupture has shown to lead to impaired knee function<sup>2</sup>, thus, restoring the dynamic knee joint stability rather than passive knee joint laxity has been considered as one of the most significant targets in the rehabilitation process after an ACL injury. The passive knee joint laxity has not been shown to be correlated with functional outcomes<sup>2, 192</sup>. Quadriceps muscle strength has been shown to be a significant factor in restoring dynamic knee joint stability after an ACL injury and reconstruction<sup>142, 174</sup>. Thus, one main factor in ACL rehabilitation today is to retain the



quadriceps strength with aggressive muscle strength protocols<sup>142</sup>. Nevertheless, quadriceps muscle deficits reaching as high as 20-40% have been detected several years after ACL injury or reconstruction<sup>89, 142</sup>. Impaired muscle function, including neuromuscular deficiencies and muscle weakness, is closely associated with impaired knee function after an ACL injury and reconstruction<sup>142</sup>. The muscles' ability to move the knee joint, to function as shock absorbers, and to maintain dynamic knee joint stability is dependent on normal muscle function<sup>26</sup>. A normal muscle function is determined by adequate muscle activation patterns of the muscle fibres<sup>26</sup>. Inhibition of the ability to activate muscle fibres as well as loss of the muscle cross-sectional area may be seen in patients with impaired muscle function after ACL reconstruction. Attention should therefore be given towards normalization of not only muscle strength, but the underlying reasons for the muscle weakness.

In addition to dynamic knee joint instability and impaired muscle function causing muscle strength deficits, joint effusion after activities has been associated with impaired knee function after ACL injuries<sup>60</sup>. For those who have undergone ACL reconstruction donor-site morbidity such as anterior knee pain after BPTB reconstruction<sup>95</sup>, reduced ROM, muscle weakness,<sup>142</sup> and neuromuscular deficits<sup>2</sup> have been detected. The literature has, however, in general reported nearly normal knee function results for the majority of the individuals who have gone through ACL surgery<sup>18, 51, 96, 108, 112, 123, 139</sup>, but also after nonoperative treatment<sup>49, 128</sup>. Lohmander et al.<sup>114</sup> reviewed knee function results in 54 long term follow-up studies, including both reconstructed and nonoperatively treated individuals. The authors detected that the knee function was reported to be good or excellent for the majority of the individuals, but only measured with the Lysholm score<sup>117</sup>. Only a few of these studies had a follow-up period beyond 10 years, and few studies had grouped the populations related to the severity of the injury. For instance, subjects with additional injury to the meniscus may have poorer knee function than subjects with isolated ACL injury. Furthermore, evaluation of knee function after an ACL reconstruction should be performed by using assessment tools that cover different aspects of knee function such as self-reported questionnaires, clinical tests, and performance-based tests (muscle strength measurements and hop tests).

## **Assessment of knee function**

Assessment of knee function following an ACL reconstruction using different assessment tools is important to identify impaired structures and functions and activity and participation limitations as further should be targeted in the rehabilitation program. Self-reported questionnaires comprise often several components related to the concept of knee function. For instance the Knee injury and Osteoarthritis Outcome Score (KOOS)<sup>163</sup> involves assessment of pain, other symptoms, activities of daily living (ADL) and sports or recreation (Sport/Rec), and knee-related quality of life (QOL). The International Knee Documentation Committee (IKDC) form<sup>82</sup>, the IKDC2000<sup>90</sup>, and the Cincinnati knee score<sup>136</sup> are other commonly used self-reporting questionnaires. The KOOS items Sport/Rec and QOL has been found to be highly relevant to detect self-reported disability in ACL reconstructed individuals<sup>78,191</sup>. Lysholm and Tegner<sup>118</sup> suggested that “separate scores for symptoms, subjective functions, and objective results should be used” for assessment of knee function. Traditionally, also clinical tests such as the KT-1000 arthrometer<sup>213</sup>, the Lachman test<sup>77</sup>, and the pivot shift test<sup>110</sup> have been included to evaluate knee function in the ACL injured population. However, passive knee joint laxity has not been shown to correlate with functional outcomes<sup>2</sup>, and should therefore only be complementary in order to evaluate knee function. Furthermore, performance-based measurements including isokinetic or isometric muscle strength tests<sup>120, 151, 4</sup> or hop tests<sup>134, 156</sup>, should be included to complement the evaluation of knee function. Implementation of muscle strength and hop tests may be of importance to assess the impact of an intervention or to reveal predisposing factors for later degenerative changes in the injured individuals<sup>120</sup>. In general, knee function assessments used for scientific purposes should be valid and reliable, and both researchers and clinicians should use the assessment tool that is most appropriate for the selected patients<sup>210</sup>.

## **Knee osteoarthritis**

Development of radiographic tibiofemoral knee osteoarthritis (in the following defined as radiographic knee OA) after ACL injuries has obtained considerable more attention than long term knee function<sup>65, 121, 124, 193, 203, 206</sup>. Lohmander et al.<sup>114</sup> did an extensive review of the literature concerning the long term prevalence of knee OA after ACL injury, including subjects with ACL injury and reconstruction. They pointed out that there was

poor methodological quality of the existing literature and therefore not possible to pool the results and perform meta-analysis. When this was taken into consideration, they estimated that approximately 50% developed symptomatic knee OA 10-20 years post-injury. Little evidence exists, however, concerning the association between radiographic knee OA, knee symptoms, and function in subjects with previous ACL reconstruction.

OA is a disorder affecting synovial joints, in particular the hip and knee, the hand and the back<sup>52</sup>. The prevalence of symptomatic knee OA in Norway is reported to be approximately 7% for people between 24-66 years<sup>74</sup>. In the US, 6% of people over 30 years has shown symptomatic knee OA, but 10-15% over 60 years are affected<sup>59</sup>. A higher prevalence of knee OA is reported for females than males after they have passed the age of 50<sup>59</sup>. The aetiology, pathogenesis, and progression of OA is not fully understood<sup>42</sup>. The structural changes appearing during the development of OA include loss of articular cartilage, remodelling and sclerosis of subchondral bone, subchondral bone cysts formation, and osteophyte formation<sup>41</sup>. Loading a structural damaged joint has been suggested to be of significant importance in the development of knee OA<sup>67, 208</sup>. The articular cartilage of the knee is divided into four layers: the superficial zone, the middle zone, the deep zone, and the subchondral bone<sup>143</sup>. Between the superficial, the middle, and the deep zones and the subchondral bone is the “tidemark” of calcified cartilage. The articular cartilage contains chondrocytes and extracellular matrix including primarily water, collagen type II, and proteoglycan<sup>143</sup>. The cartilage has low metabolic activity, lacks blood supply and innervation, and the regenerative capacity has been shown to be poor<sup>72, 143</sup>. The cartilage has highly specialized tissue with unique mechanical behaviour and low-friction abilities customized to bear and distribute loads<sup>143</sup>. Below the cartilage lies the calcified bone which includes the subchondral bone plate, the subchondral trabecular bone, and the bone located at the joint margins<sup>68</sup>. Osteoclast cells and osteoblast cells work together to sustain the equilibrium of bone mass, and such permit adaptation of the bone structure to mechanical loading<sup>68</sup>. It has been suggested that the superficial zone of the cartilage is first affected in the development of OA, and that loss of proteoglycan content appears early<sup>143</sup>. It has also been suggested that OA is a disease initiated in any of the tissues in the affected joint<sup>34,119</sup>. Mild synovitis and thickening of the joint capsule have also been seen in OA joints<sup>52</sup>. Studies have shown that excessive mechanical loading can alter chondrocyte function<sup>87</sup>, and thus the chondrocytes fails to maintain the balance between synthesis

and degradation of the extracellular matrix, in particular for the proteoglycan content<sup>66</sup>. Consequently, cartilage surface fibrillation, cleft formation, and cartilage loss may appear<sup>52</sup>. A typical feature seen in OA is the presence of osteophytes at the joint margins which seem to develop through endochondral ossification<sup>68</sup>. Nevertheless, it is not documented where in the course of the OA disease the osteophytes develop<sup>52</sup>.

The patients may experience these structural changes as increased pain or other symptoms in the knee. A typical OA patient is above 40-50 years of age, has joint pain related to use, and may experience short lasting morning stiffness, joint crepitus, and muscle weakness<sup>52</sup>. Disagreement exists in the literature with respect to the association between structural changes and knee pain<sup>22</sup>, and studies are lacking concerning knee injured patients. It is believed that the natural course of OA includes progression of the disease, however it is also pointed out that progression may not always occur<sup>52</sup>. There is limited knowledge with regard to OA progression in subjects with ACL reconstruction.

### **Diagnosis of knee osteoarthritis**

After many years of research and development of clinical knowledge within the field of OA there is still not consensus regarding the diagnosis of knee OA. Knee OA is basically determined on the basis of radiographic abnormalities alone or in combination with clinical findings such as pain, effusion, and crepitus<sup>11, 98</sup>. As most people with OA seek medical care because of joint pain, a diagnosis of OA is often verified by additional radiographic abnormalities. Different radiographic atlases exist with description of abnormalities and grades of OA<sup>1, 12</sup>. Conventional x-rays show bone abnormalities such as osteophytes, subchondral sclerosis, subchondral cysts, and damage to cartilage indirectly through joint space narrowing (JSN). Although the Kellgren and Lawrence (K&L) classification<sup>1, 98</sup> for radiographic changes in the joints is frequently used, criticism has been raised against this system as well. For instance, several versions of the system are in use<sup>171</sup>, and the cutoff grade for defining radiographic knee OA (grade 2) emphasizes osteophyte formation more than JSN. Other classifications frequently used include the Osteoarthritis Research Society International (OARSI) atlas<sup>12, 13</sup>, the Ahlbäck classification<sup>7</sup>, and the IKDC classification<sup>90</sup>. The cutoff for defining knee OA in these classifications includes JSN of about 50% (2-4 mm).

The radiographic examination involves standing weight-bearing position with the knees flexed or extended. Buckland-Wright et al.<sup>39</sup> evaluated different positions during

the radiographic examination and concluded that semi-flexed position gave the best x-rays to consider for knee OA. In the semi-flexed view the site of measurement is at the middle of the tibial plateau, consistent with the region of normal functional loading of the joint. Osteophytes formation, JSN, sclerosis, and bone deformations are structural changes examined on the x-rays<sup>7, 12, 90, 98</sup>. Measurement of joint space width (JSW) may be performed with a ruler, a magnifying lens, callipers, or computer programs. Computer programs are suggested to overcome the limitations of observer variability providing reproducible and an accurate method for measuring JSW<sup>38, 75</sup>. An average annual JSN in knees with OA are found to be 0.10-0.15 mm<sup>56, 75</sup>, however, the JSW has also been shown to decrease with age<sup>64</sup>.

The definition of *symptomatic* radiographic knee OA includes evaluation of knee pain or symptoms in addition to the radiographic abnormalities. The American College of Rheumatology (ACR)<sup>11</sup> clinical and radiographic criteria for knee OA include knee pain and osteophytes plus at least one of three other criteria: age more than 50 years, morning stiffness less than 30 minutes, or crepitus. Peat et al.<sup>144</sup> evaluated the association between the ACR criteria and symptomatic radiographic knee OA defined by knee pain on most days the last months plus radiographic abnormalities. They found low agreement between these two methods, and concluded that the ACR criteria seemed to reflect the more severe grades of OA.

### **From anterior cruciate ligament injury to knee osteoarthritis**

Knee injuries, in particularly ACL and/or meniscus injuries, have been shown to be of great importance for development of tibiofemoral knee OA<sup>63, 84, 164</sup>. The link from an ACL injury to development of knee OA, both for individuals treated nonoperatively and for those treated with reconstruction, has obtained more attention the last years as more follow-up studies exist. However, the mechanism behind the development of OA in these subjects is not fully understood<sup>42</sup>. Studies have suggested that changes in knee joint loading due to muscle weakness after the injury, in particularly quadriceps weakness, and consequently decreased dynamic knee joint stability causes development of knee OA<sup>141, 188</sup>. The quadriceps muscle works as a shock absorber for knee joint loading during activities in the upraised position. Muscle weakness reduces the ability to shock absorb, and as a consequence alter the loading conditions during activity. The loads acting in the knee joint have been related to the external knee adduction moment and

the internal moment that counteract to the external adduction moment<sup>43</sup>. Muscles as well as ligaments, menisci, and capsule have been shown to contribute to the internal abduction moment, with quadriceps muscle strength as one of the main contributors<sup>141</sup>. The greater loads in the knee joint may result in cumulative microdamage in the cartilage or the subchondral bone<sup>33, 141</sup>.

The mechanism behind quadriceps weakness after ACL injury has been suggested to be due to inactivity atrophy and/or arthrogenic muscle inhibition (AMI)<sup>26</sup>. The ACL provides sensory information during joint motion to the CNS. After an injury, however, this pathway seems to be disturbed, resulting in a decreased excitability of the alpha motoneurons to activate the quadriceps<sup>141,101</sup>. Some studies have demonstrated that quadriceps weakness seems to be a risk factor for the initiation of knee OA<sup>86, 183, 175</sup>, but no prospective long term studies including subjects with ACL injuries have examined the association between quadriceps weakness and knee OA.

Several risk factors for development of knee OA have been reported in the literature. The risk factors are often referred to as either systemic, intrinsic, or extrinsic risk factors<sup>59</sup>. The systemic risk factors include genetics, age, gender, and nutritional factors. The intrinsic and extrinsic variables involve joint injuries, malalignment, obesity, muscle weakness, and inappropriate loading in occupational or sports activities<sup>59</sup>. Risk factors that have been shown to influence the development of knee OA following an ACL reconstruction include: increased age at the time of the injury, additional meniscal tears with subsequent meniscectomy, chondral lesions, and BPTB graft<sup>57, 97</sup>. Very few high quality studies have examining risk factors for development of knee OA following an ACL reconstruction. To be able to prevent the high prevalence of tibiofemoral knee OA seen in subjects with knee injuries, large risk factor studies are needed.

## **Aims of the thesis**

The overall aim of this thesis was to examine the long term consequences of ACL injury and reconstruction with emphasize on the prevalence of knee OA, knee function, the association between radiographic knee OA, knee symptoms and function, and the risk factors for knee OA. The specific aims were:

- I. To evaluate the prevalence of radiographic and symptomatic radiographic OA in the tibiofemoral joint more than 10 years after ACL injury and ACL reconstruction (Paper I and II)
- II. To compare knee function outcomes over time in individuals with isolated ACL injury to individuals with combined injury (Paper II)
- III. To examine the association between radiographic knee OA and knee symptoms, knee function, and knee-related quality of life, respectively, 10-15 years after ACL reconstruction (Paper III)
- IV. To investigate risk factors associated with knee OA more than 10 years after ACL injury and reconstruction (Paper I and IV)

## **Material and methods**

### **Ethical considerations**

All subjects included in this thesis (Paper II-IV) signed an informed written consent before participation at the 10-15 year follow-up. The informed consent included information regarding the clinical and functional examination. The study participants were informed that no health risks were associated with participation in the study. Pregnant women did not go through the radiographic examination. The study was approved by the National Committees for Research Ethics in Norway and The Data Inspectorate (Personvernombudet). The rights of the participants are protected by the ethical principles stated in the Declaration of Helsinki.

### **Study materials**

The four Papers included in this thesis consist of one systematic review (Paper I), two prospective cohort studies (Paper II and IV), and one cross-sectional study (Paper III). The study material in the systematic review (Paper I) comprise 31 studies with a follow-up time of at least 10 years including subjects who had suffered an ACL injury. Papers II, III, and IV consist of study participants from four separate studies included in the period from 1990 to 1997. A total of 258 subjects reconstructed with either BPTB or HT grafts were included with similar inclusion and exclusion criteria; therefore, the subjects have been regarded as one prospective cohort. Several studies have previously been published from the material with two years follow-up<sup>19, 85, 159-161</sup>. A flow chart of the study participants is presented in Figure 1. The inclusion and exclusion criteria for the studies are described in Figure 2.

#### *Paper I*

The inclusion criteria for the systematic review were studies involving: subjects with an ACL injury; both surgical and non-surgical treatment; more than 10 years follow-up; prospective or retrospective study designs, and studies including radiographic examination of the study participants. A total of 3069 subjects with ACL injury were included in the 31 studies.



### *Paper II*

Paper II included 181 of a total of 221 subjects (82%) reconstructed with BPTB graft. The study included 76 (42%) females and 105 (58%) males with mean age of  $39.5 \pm 8.6$  years at the 10-15 year follow-up. The mean (Standard deviation, SD) body mass index (BMI) was 25.2 (3.0) at the 10-15 year follow-up. The mean time between injury and surgery was  $28 \pm 52$  months.

### *Paper III*

All the subjects available for the 10-15 year follow-up were included in Paper III ( $n=210$ )(81%). Of the 210 subjects, 90 (43%) were females and 120 (57%) were males. The mean age was  $39.1 \pm 8.7$  years, and the mean time between injury and surgery was  $24.8 \pm 48.7$  months. The mean (SD) BMI was 26.3 (3.6) at the 10-15 year follow-up.

### *Paper IV*

In Paper IV we excluded subjects who had suffered injuries to the contralateral knee during the follow-up period ( $n=46$ ). Thus, only subjects with unilateral injuries were included ( $n=164$ ). There were 71 (43%) females and 92 (57%) males included in Paper IV with mean age of  $27.4 \pm 9.7$  years at the time of ACL reconstruction. The mean (SD) BMI was 26.3 (3.8) at the 10-15 year follow-up. The mean time between injury and ACL reconstruction was  $27.2 \pm 53$  months.

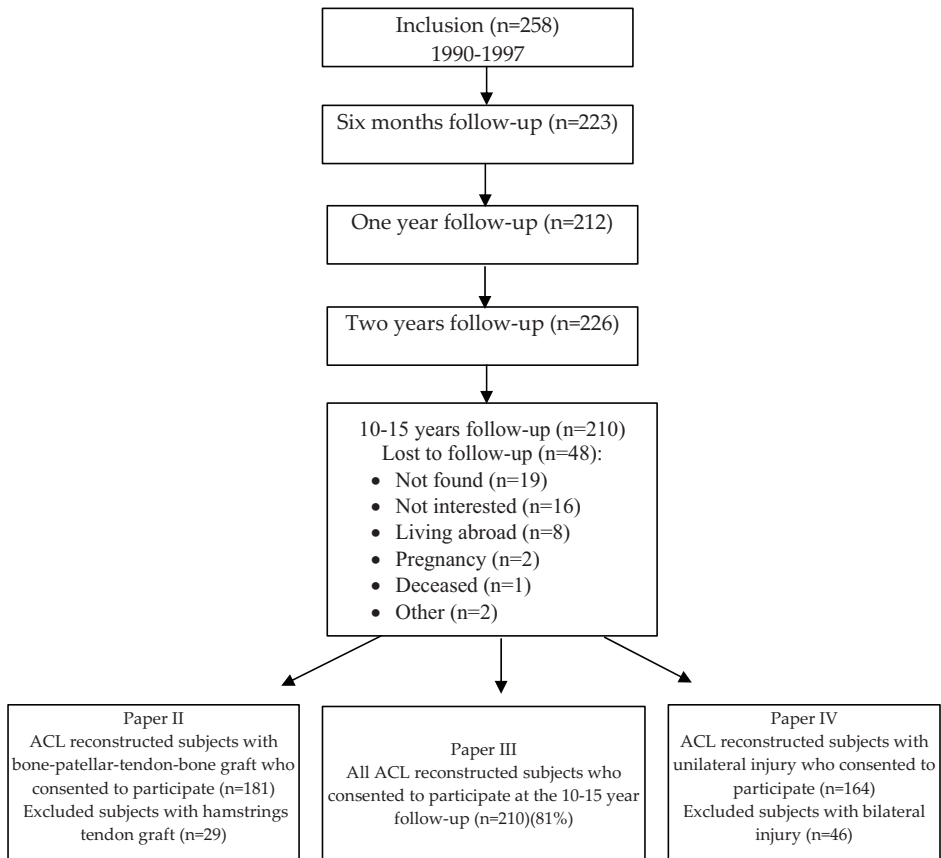


Figure 1. Flow chart of the subjects included in the 10-15 year follow-up study for Paper II, III, and IV.

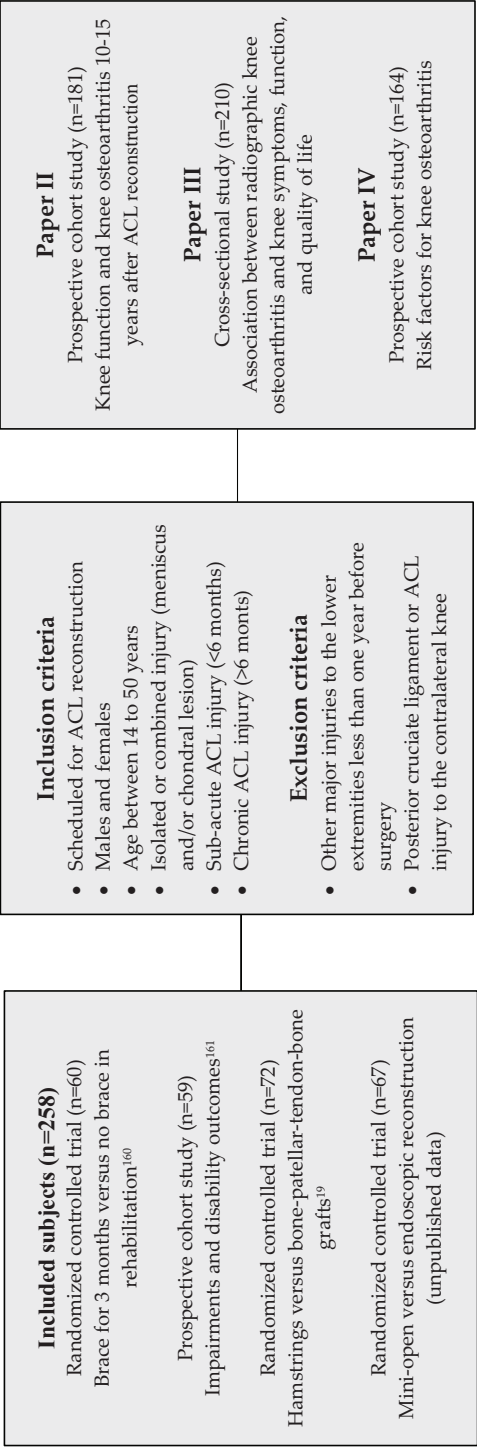


Figure 2. Number of included subjects in original studies with inclusion and exclusion criteria and the number of included subjects at the 10-15 year follow-up for Paper II, III, and IV.

## **Outcome measurements**

The outcome measurements for Paper II-IV are shown in Table 1. Paper I included the Coleman Methodology Score (CMS)<sup>47</sup> to evaluate methodologic quality of the studies. The CMS were based on the Consolidated Standards of Reporting Trials (CONSORT) statement for RCTs<sup>10</sup>, therefore we modified the original score to be suitable for cohort studies.

### *Knee function*

The Cincinnati knee score have been included at all the follow-ups (6 months, 1 year, 2 years, and 10-15 years) to measure self-reported knee function. This questionnaire includes evaluation of pain, swelling, giving way, general activity level, walking, stair climbing, running, jumping, and twisting activities<sup>135</sup>. This self-reported questionnaire has been shown to be sensitive to changes over time in subjects with ACL injury<sup>159</sup>, and it has showed to report functional outcomes accurately<sup>180</sup>. The extended version of the Cincinnati knee score has shown good reliability and validity<sup>21</sup>. After the start of inclusion of participants in this study other validated self-reported outcomes for posttraumatic knee OA have been published. Therefore, the KOOS questionnaire<sup>163</sup> was only included at the 10-15 year follow-up. This questionnaire consists of five subscales on pain, other symptoms, ADL, Sports/Rec activities, and QOL. This self-reported questionnaire has been validated for use in subjects with ACL injury and posttraumatic OA<sup>165, 166</sup>. A visual analogue scale (VAS)(0-10 mm) validated for measuring pain<sup>149</sup> was included for assessment of pain during rest and during or after activity at the 10-15 year follow-up. The subjects drew a mark on a line where 0 mm indicated no pain, whereas 10 mm indicated worst pain. The Tegner activity scale (0-10) was included at the 10-15 year follow-up<sup>194</sup>. Zero points indicates sick leave or disability pension, and 10 points indicate participation in competitive sports including soccer, football, team handball, and other high level pivoting activities. The Tegner activity scale has shown acceptable validity and reliability in subjects with ACL and meniscal injuries<sup>35, 92</sup>. The subjects were retrospectively asked at the 10-15 year follow-up about return to sports after the ACL reconstruction. This question was recorded as a dichotomous variable (yes/no).

The KT-1000 knee arthrometer (MED metric Corp., San Diego, California) was included using the manual maximum test to record anterior displacement of the tibia in relation to the femur. This test was included at all the follow-ups. Satisfactory reliability

has been reported for this test for patients with ACL injury<sup>15, 20, 27, 79</sup>. The Lachman test<sup>76, 77, 48</sup> and the pivot shift test<sup>91, 110</sup> were included at the 10-15 year follow-up for additional tests of knee joint laxity. The Lachman test has been validated to determine ACL tears and the pivot shift test has shown good specificity, but poor sensitivity on both acute and chronic ACL injuries<sup>24</sup>.

Isokinetic muscle strength tests were included at all follow-ups to evaluate muscle strength for the hamstrings and quadriceps muscles (Cybex 6000, Cybex Lumec Inc, Ronkonkoma, NY, USA) and performed by the same Physical therapist (PT). The muscle strength test included a 5 minutes warm-up session on a stationary ergometer cycle followed by concentric measurements of total work (TW) in Joules (J) at 60°/sec and 240°/sec with 5 and 30 repetitions, respectively. Isokinetic muscle tests have shown good reliability for strength measurements in normal subjects<sup>111, 147</sup>, in physically active subjects<sup>88</sup>, and in patients with ACL reconstruction<sup>36, 151</sup>. Furthermore, it has been shown to be suitable for assessing strength in individuals with early knee OA<sup>53</sup>. The triple jump test<sup>134</sup> and the stair hop test<sup>158</sup> were included at all the follow-ups to measure knee function. The triple jump test and the stair hop test have been shown to be valid and reliable for healthy athletes and for subjects that have undergone ACL reconstruction<sup>156, 158</sup>.

### *Knee osteoarthritis*

The radiographic assessment at the 10-15 year follow-up was performed using the SynaFlexer frame for standardized positioning (Synarc, Inc, Copenhagen, Denmark) as described by Kothari et al<sup>103</sup>. A standardized degree of knee flexion (20°) and external foot rotation (5°) are achieved with use of the frame. The frame is validated for measurement of JSW in patients with knee OA<sup>103</sup>. X-rays were taken in the posteroanterior view in the frontal plane, bilaterally.

The K&L classification was used for grading the radiographs of the tibiofemoral joint<sup>98</sup>. In this system, the severity of radiographic changes is graded from 0 to 4. Grade 0 corresponds to no changes; grade 1 to doubtful narrowing of joint space and possible osteophytic lipping (doubtful); grade 2 to definite osteophytes and possible narrowing of joint space (mild); grade 3 to moderate multiple osteophytes, definite narrowing of joint space, and some sclerosis, and possible deformity of bone ends (moderate), and grade 4 to large osteophytes, marked JSN, severe sclerosis, and definite deformity of

bone ends (severe). This corresponds to the version of K&L classification from 1963<sup>1</sup> which is based on the original study from 1957. Grade  $\geq 2$  was used as cutoff for defining radiographic knee OA in the present study, according to previous literature on OA<sup>171</sup>. For defining symptomatic radiographic knee OA, the individuals were asked if they had experienced pain in the knee during the last month (yes/no). Those who answered yes to this question and additionally had a K&L grade  $\geq 2$ , were classified as having symptomatic radiographic OA.

Intrarater reliability test was performed by the radiologist and interrater reliability test was performed by the radiologist and one orthopaedic surgeon on 35 of the x-rays, including both knees (n=70). These tests were performed with at least a four week interval between the tests.

**Table 1. Outcome measurements in Paper II, III, and IV**

| Paper II-IV  | Outcome measurements   |
|--|--|
| <p><b>Paper II</b></p> <p>Knee function and prevalence of knee osteoarthritis after anterior cruciate ligament reconstruction. A prospective study with 10-15 years follow-up</p>                    | <p>Knee symptoms and function</p> <ul style="list-style-type: none"> <li>• Cincinnati knee score</li> <li>• Visual analogue scale for pain</li> <li>• Tegner activity scale</li> <li>• KT-1000 manual maximum test</li> <li>• Lachman test</li> <li>• Pivot shift test</li> <li>• Isokinetic muscle strength tests</li> <li>• Triple jump test</li> <li>• Stair hop test</li> </ul> <p>Knee osteoarthritis</p> <ul style="list-style-type: none"> <li>• Kellgren and Lawrence classification</li> <li>• Kellgren and Lawrence scores + knee pain</li> </ul>  |
| <p><b>Paper III</b></p> <p>The association between radiographic knee osteoarthritis and knee symptoms, function, and quality of life 10-15 years after anterior cruciate ligament reconstruction</p> | <p>Knee symptoms, function, and quality of life</p> <ul style="list-style-type: none"> <li>• Knee Injury and Osteoarthritis Outcome Score</li> </ul> <p>Knee osteoarthritis</p> <ul style="list-style-type: none"> <li>• Kellgren and Lawrence classification</li> </ul>   |
| <p><b>Paper IV</b></p> <p>Quadriceps muscle weakness after anterior cruciate ligament reconstruction: a risk factor for knee osteoarthritis?</p>   | <p>Independent variables:</p> <ul style="list-style-type: none"> <li>• Body weight</li> <li>• Body mass index</li> <li>• Additional injuries to the menisci/cartilage/medial collateral ligament</li> <li>• Graft type</li> <li>• Time between injury and surgery</li> <li>• KT-1000 manual maximum test</li> <li>• Cincinnati knee score</li> <li>• Isokinetic muscle strength test</li> <li>• Triple jump test</li> <li>• Stair hop test</li> </ul> <p>Dependent variables:</p> <ul style="list-style-type: none"> <li>• Kellgren and Lawrence scores</li> <li>• Kellgren and Lawrence scores + knee pain</li> </ul> |

## Statistical methods

Descriptive statistics were presented as means and SD or frequencies (%) in all the studies. A p-value of less than 0.05 was considered statistical significant for all the analyses. Statistical Package for Social Sciences (version 16.0, SPSS, Chicago, Illinois) was used for all the statistical analyses.

### *Paper II*

The variables were tested for normality with the Kolmogorov-Smirnov test. The analysis of variance (ANOVA) two-way mixed between groups and within subject model was used to test changes over time for BMI, the KT-1000 manual maximum test, and the knee function outcomes (The Cincinnati knee score, the muscle strength tests, and the hop tests). The analyses included comparison between subjects with isolated and combined ACL injury (those with combined injury had meniscal injury and/or chondral lesion, and/or MCL injury, or only chondral lesion grade III or IV). Bonferroni post hoc test was used to examine the significance level between the specific time points. The Cincinnati knee scores were not normally distributed. Therefore, the Friedman test was used to test for changes between specific time points. Student's t-test and Mann Whitney U test were used for group comparisons when normality was accepted or rejected, respectively. Chi-square test was used for comparison of categorical variables. Kappa (k) statistics was used for examining inter- and intrarater observer reliability of the radiographs.

### *Paper III*

Linear regression analysis was included to assess the relationship between the dependent variables (the KOOS subscales) and the independent variables (radiographic knee OA and control variables). The regression analysis was presented both as unadjusted values and adjusted for age, gender, and BMI. Multivariate regression analysis was included for assessment of the relationship between each KOOS subscale (dependent variables) and the different K&L grades which were converted to dichotomous variables (grade 2 versus grade 0, grade 3 versus grade 0, and grade 4 versus grade 0, respectively). K&L grade 0 and 1 were collapsed and used as reference category (Grade 0). These analyses were adjusted for gender, age, and BMI. Mann



Whitney U test was included to perform group comparisons of nonparametric data (Tegner activity scale). Intrarater observer reliability of the radiographs were analysed using k statistic.

#### *Paper IV*

The Chi-square test and the Mann Whitney U test were used for group comparisons of nonparametric data. Binary logistic regression analyses presenting odds ratio (OR) and 95% confidence interval (CI) were performed for identification of risk factors and predictors for radiographic and symptomatic radiographic knee OA, respectively. Both univariate and multivariate models were included to be able to identify the variables that should be included in the final regression models. A p-value of <0.20 was set to include the independent variable from the univariate analysis into the adjusted analysis, and thereafter a p-value of <0.05 was set to include the independent variable into the final logistic regression model.

## **Summary of results**

### **Paper I**

A total of 31 studies were included in the systematic review. Seven studies had prospective design and 24 had retrospective design. A mean modified Coleman Methodology score showed 52 of a total of 90 points, with a mean of 69 and 47 points for the prospective and retrospective studies, respectively. The prevalence of radiographic knee OA for studies with best methodological score was between 0 to 13% for subjects with isolated ACL injury, and between 21 to 48% for subjects with combined ACL with meniscus and/or MCL injury. Seven radiographic classification systems were used including: the K&L classification, the Ahlbäck classification, the IKDC classification, the OARSI atlas, the Fairbank sign, an atlas including a combination of osteophytes and JSN, and a combination of the Fairbank sign and the Ahlbäck classification. Only three of the 31 studies reported reliability results for the radiographic scorings. Risk factors for development of knee OA in studies using regression analysis were reported to be meniscal injuries, ACL surgery, increased age at surgery, increased BMI, <90% on single-legged hop test compared to the contralateral knee 1 year after the surgery, loss of extension in ROM, and increased knee joint laxity. In addition, the other studies which used group comparisons, reported additional risk factors to be: more than 6 months between the ACL injury and surgery, high level of sports activity, OA in the contralateral knee, and increased time to follow-up.

### **Paper II**

The knee function outcomes including the Cincinnati knee score and the isokinetic quadriceps and hamstrings muscle strength tests revealed significant improvement from 6 months to 10-15 years after the ACL reconstruction. Furthermore, no group differences were detected in self-reported knee function or muscle strength over time for those with isolated ACL injury compared to those with combined ACL with meniscal injury and/or MCL injury, and/or chondral lesion. Seventy-four percent of the subjects had knee OA according to K&L  $\geq$  grade 2, and 41% had symptomatic radiographic knee OA according to K&L  $\geq$  grade 2 and knee pain. Significantly higher prevalence of knee OA was found for subjects with combined injury than for subjects with isolated ACL injury

(80% and 62%) ( $p=0.008$ ). The difference between those with isolated compared to combined injury for symptomatic radiographic knee OA was not significant (46% and 32%) ( $p=0.053$ ).

### **Paper III**

No significant association was detected between radiographic knee OA ( $K\&L\geq 2$ ) and knee pain, function, or knee-related quality of life, controlled for gender, age, and BMI. A significant association between radiographic knee OA and other symptoms was found. Significant associations were detected between severe radiographic knee OA ( $K\&L$  grade 4) and pain, other symptoms, ADL, Sport/Rec, and QOL adjusted for gender, age, and BMI.

### **Paper IV**

Our data detected no significant associations between quadriceps muscle weakness up to 2 years after ACL reconstruction and radiographic knee OA. The risk factors that were identified for radiographic knee OA included increased age at the time of ACL reconstruction and additional meniscal and/or chondral injury and/or MCL injury at the time of ACL reconstruction or suffered during the follow-up period. No risk factors were significantly associated with symptomatic radiographic knee OA. But those with impaired self-reported knee function at 2 years postoperatively and those who lost quadriceps muscle strength between the 2 year and the 10-15 year follow-up showed significantly higher odds for symptomatic radiographic knee OA.

## Discussion

The overall aim of this thesis was to examine the long term consequences after ACL reconstruction with emphasis on the prevalence of knee OA, knee function, the association between radiographic knee OA, knee symptoms and function, and the risk factors for knee OA. In the following a discussion with respect to the study design, the results, the conclusions, and the clinical and future perspectives is given.

### Methodological considerations

Observational study designs have been the most frequently used and probably also the most accessible research method in orthopaedic studies<sup>30</sup>. Performing RCTs in orthopaedic research may not always be practical, feasible, or ethical. Most of the existing long term follow-up studies on subjects with ACL injury are cohort studies, with either retrospective<sup>46, 81, 83, 99, 115, 121, 130, 170, 177-179, 181, 187, 201, 205, 215</sup> or prospective designs<sup>54, 80, 109, 125, 133, 148, 214, 169, 206</sup>, but also a few RCTs exist<sup>125, 148</sup>. Cohort studies are characterized by observation of interventions, exposures, or outcomes over time as they occur naturally from the time of inclusion<sup>37</sup>. A case-control design also incorporate observation of a control group without the exposure of interest. The weaknesses which potentially may influence the internal validity of cohort studies include first and foremost selection bias, confounding factors, and loss to follow-up.

The prospective cohort study design is the most adequate design for evaluating long term knee function and development of knee OA in subjects with ACL injury and reconstruction. The prospective cohort included in this thesis was originally three RCTs and one prospective cohort all with 2 years follow-up. The inclusion and exclusion criteria were almost identical for the four studies. Furthermore, there were no significant differences between groups with respect to knee function outcomes up to 2 years after ACL reconstruction<sup>19, 160</sup>. We also excluded HT graft and controlled for graft type in Paper II and IV, respectively, to control for potential differences between the groups. In addition, the same clinical and functional outcomes were used and assessments were performed by the same research team. Based on the above mentioned factors, we have merged the 258 subjects from the four original studies into one prospective cohort of subjects. A weakness with the study is the lack of prospective data on both radiographic and symptomatic radiographic knee OA. We may, nevertheless,

assume that the included study participants had very low prevalence of OA before the ACL injury, based on their young age and also based on few cases with deep chondral lesions (n=11) reported in the surgical files. Also pre-injury and pre-surgical examination of knee function and knee OA would have strengthened our data. Except from the radiographic evaluation, all clinical and functional data were prospectively collected from 6 months postoperatively to the 10-15 year follow-up.

None of the prospective studies evaluated in the systematic review (Paper I) included a control group other than the contralateral knee. This may be explained by the additional costs and resources needed to include a healthy control group, but also the fact that most of the studies had a retrospective study design. The uninjured contralateral knees were also used as controls in our studies (Paper II and IV). The contralateral knee may be an adequate control due to the automatic matching of components such as age, gender, weight, BMI, activity level, or genetic factors which may influence the development of knee OA. The criticism of using the contralateral knee as control may be that also this knee may have altered loading due to the injury in the opposite knee<sup>89</sup>. The prevalence of knee OA in the uninjured knees in our cohort was 14% (Paper IV) indicating that this number is higher than the estimated number for uninjured knees in the same age group (1-2%)<sup>65, 107</sup>. Therefore, to use the contralateral knee as control may not provide the most accurate results compared to a matched healthy control group. Historical or concurrent comparison groups are most used, but selection bias may cause incorrect results<sup>37</sup>.

The follow-up rate of the study participants is another important methodological issue related to long term follow-up studies in terms of selection bias. The consequences of loss to follow-up may be dependent of if the loss of subjects is missing at random or is systematic missing. A systematic loss to follow-up of 20% has been associated with considerable bias<sup>104</sup>. Random loss to follow-up of up to 60% has been shown to give unbiased results<sup>104</sup>. In RCTs a loss to follow-up greater than 20% has been suggested to threaten the validity of the study<sup>173</sup>. Difficulties with respect to finding the study participants after several years and to motivate them to participate, and furthermore the costs related to participation for those who live long distance away may cause low follow-up rates. The follow-up rate in the present study was 81% (Paper II-IV). Taken the long term follow-up time into consideration, a loss to follow-up of 19% may be considered as acceptable in the relative large cohort. The main reasons for the loss to

follow-up in our study included subjects not found (7%), or that they were not interested in participating (6%). Those who were not interested in participating in the 10-15 year evaluation explained this with busy schedules. Consequently, their knees may have functioned well, and the loss to follow-up may have biased the results. But those missing due to busy schedules constituted only 6% of the cohort and this may not have threatened the validity of the study. Drop-out analyses were performed on data from the 6 months, the 1 year, and the 2 year tests, and no differences were detected between those who did not participate at the 10-15 year follow-up and those who participated with respect to age and gender.

Confounders are variables that are associated both with the explanatory variable and with the outcome, and may therefore influence the association between the explanatory variable and the outcome variable<sup>37, 126</sup>. Methods for reducing confounding effects in cohort studies may be to restrict inclusion and exclusion criteria, and therefore study a more homogenous sample. However, this may contrarily threaten the external validity of the results<sup>37</sup>. Confounding factors with regard to ACL injuries and knee OA may be difficult to identify. In Paper IV we aimed at identify risk factors for development of both radiographic and symptomatic radiographic knee OA in subjects with ACL reconstruction. The study population (n=164) may have been too small to detect many risk factors for knee OA, and there may have existed confounders that we were not able to include in the analyses such as genetic factors that may predispose for OA and data on type or level of activities.

## **Subjects**

The subjects included in the present cohort study were scheduled for ACL reconstruction at three different hospitals in the Oslo region and were consecutively included in the four original studies. The mean age at surgery was 27 years, and the mean age at follow-up was 39 years. The mean age at follow-up for the studies in the systematic review was also 39 years. Furthermore, in Paper II, we detected that 60% had additional injuries at the 10-15 year follow-up, including about 50% of the additional injuries detected at the time of the ACL reconstruction. The data on additional injuries have been retrospectively extracted from surgeon files and may have been underestimated. However, additional meniscal injuries have been detected to be about 50% at the time of surgery in ACL registry studies<sup>69</sup>. The distribution of females and

males in our cohort (Paper II) can be compared to the cohorts included in the systematic review (Paper I), with an overrepresentation of males in all the cohorts. Unfortunately, our data did not include prospective data on the activity level. About 60% of the subjects were injured while playing ball sports, and in Paper II we detected retrospectively that 50% of the individuals returned to ball sports (n=92). Participating in soccer and team handball play may be risk factors for suffering an ACL injury, and soccer play has been associated with development of knee OA in itself<sup>167</sup>. Therefore, activity may be a confounding factor in the association between ACL injury and development of knee OA. Low prevalence of knee OA has been found in long term follow-up studies concerning ACL injured subjects that have been counselled to modify their activity level after the injury<sup>133</sup>. The long term activity level in the present study (Tegner score of 4) seems to be quite similar compared to other long term follow-up studies (Tegner score of 5). On the basis of the descriptive data our cohort may be considered as a representative sample of an ACL population which is important with respect to the external validity of the study.

### **Outcome measures**

The assessment of knee function in the present study included both self-reported questionnaires (The Cincinnati knee score and the KOOS), clinical tests (the KT-1000 manual maximum test, the Lachman test, and the pivot shift test), and performance-based tests (isokinetic muscle strength tests and hop tests). The most used assessment tool to measure knee function in the ACL injured population has been shown to be the Lysholm score<sup>114</sup>. We included the Cincinnati knee score<sup>135</sup> at all follow-ups (Paper II and IV) to evaluate self-reported knee function. This score incorporates both symptoms and function and has previously been detected to be sensitive to changes over time in the ACL reconstructed population<sup>159</sup>, and has shown to be similar to the IKDC2000 in measuring overall knee function limitations<sup>6</sup>. However, this score was developed for use on the ACL injured population. Thus, we included the KOOS score at the 10-15 year follow-up to evaluate knee function in subjects with knee OA. Hambly and Griva<sup>78</sup> found that the KOOS subscales related to activity and participation (KOOS Sport/Rec and QOL) were highly important in subjects who had undergone ACL reconstruction. Furthermore, they found that the KOOS other symptoms subscale seemed to be more important in this population than the Pain and the ADL subscales in line with the mean KOOS values as

shown in Paper III (Table 1). The average ACL reconstructed individual seems to rate pain and ADL activities of less importance than other symptoms. However, the authors<sup>78</sup> also noted that the KOOS other symptoms was not experienced as very important in ACL reconstructed subjects. Their results may nevertheless not be directly comparable to our results due to the shorter follow-up time in their study (mean time from surgery was 11 months).

Clinical tests have traditionally been included as diagnostic tools for ACL injured subjects, but also as outcomes after ACL reconstruction as knee joint stability has been the main target of ACL surgery. Evaluation of clinical tests in long term follow-up studies after ACL reconstruction may be of limited value<sup>17</sup>, but may be included as complementary tools in case of re-ruptures or if the subjects suffer from episodes of giving way.

Incorporating muscle strength tests and hop tests following ACL reconstruction give significant information regarding the functional limitations of the patients. The patients may report nearly normal knee function based on a self-reported questionnaire, but the strength that is required to return to sport in particular on a competitive level may still be too low. Results from muscle strength and hop tests are valuable in the short term after an ACL reconstruction, but muscle strength tests should also be performed in the long term as quadriceps weakness has been suggested to be a risk factor for development of knee OA<sup>141, 182, 183, 196</sup>. The implementation of the self-reported questionnaires, the clinical tests, and the performance-based tests in the present thesis seem to be satisfactory to assess the construct of knee function.

Evaluation of tibiofemoral knee OA with plain radiographs was the main outcome throughout the studies presented in this thesis. The K&L classification emphasizes appearance of osteophytes as an indicator for mild OA<sup>98</sup>. There has been criticism of using osteophytes to define OA. It has been suggested that the development of osteophytes alone does not justify the diagnosis of OA, because athletes may develop osteophytes without other aspects of degeneration<sup>40</sup>. It has also controversially been stated that osteophyte formation rather is an indication of healthy tissue than a disease, due to its ability to rebuild new healthy tissue<sup>153</sup>. Nevertheless, established OA are also characterized by JSN, sclerosis, and deformity of bone. Furthermore, newer radiographic classification systems emphasize the measurement of JSW in defining knee OA. Both the OARSI atlas<sup>12</sup>, the Ahlbäck classification<sup>7</sup>, and the IKDC classification<sup>82</sup> include JSN for



defining knee OA. However, the OARSI atlas involves grading of individual findings, such that individuals with OA may be defined both by osteophytes only or by JSN only, or a combination. The K&L classification has been widely used to define OA and is still considered being one of the most valid methods to define knee OA<sup>172</sup>. To be able to compare results across studies and state firm conclusions of the prevalence of knee OA, all studies should use the same classification system. Using several classifications, we need to compare K&L grade 3 and 4 with the classifications that define OA on the basis of JSN. A moderate correlation has been found between the K&L classification and articular cartilage degeneration as verified through arthroscopy, and there has been suggested in the literature that imaging methods that are more sensitive than standard radiographs should be used to define knee OA<sup>100</sup>. In addition, increased proteoglycan content and increased cleavage of type II collagen subsequent to an ACL injury has been shown to be associated with radiographic knee OA<sup>131</sup>. New technology (non-invasive techniques) in particular within magnetic resonance imaging (MRI) will probably in the future give us more information on the onset and development of knee OA.

The diagnosis of knee OA often includes radiographs, but also evaluation of clinical findings, such as pain, is essential for the diagnosis of OA since OA is a clinical syndrome. There exists no clear definition of what OA is. Traditionally, only radiographic OA has been included in long term follow-up studies of subjects with ACL reconstruction. However, those who seek medical care have knee pain, but not always abnormal radiographs. Therefore, the present thesis has also included symptomatic radiographic OA and the risk factors associated with symptomatic radiographic OA in individuals with ACL reconstruction (Paper II-IV) by asking the patients about knee pain during the last 4 weeks (at the 10-15 year follow-up). The definition of symptomatic radiographic OA is usually determined by asking the individuals about knee pain on most days during a given time period in addition to radiographic abnormalities according to the cut off for OA<sup>144, 168</sup>. Knee pain has been shown to be strongly associated with osteophytes<sup>184</sup>. Knee pain associated with OA may however fluctuate, and the time period of the assessment may influence the result. Furthermore, many factors may influence the experience of pain, for instance coping strategies and sociocultural environment<sup>132</sup>. Knee pain may also be derived from other structures than the degenerative changes, for instance, subjects with BPTB have reported anterior knee pain<sup>31</sup>. Toivanen et al.<sup>197</sup> studied the agreement between clinical diagnosis of OA

including ROM, tenderness, deformation, effusion, pain, stiffness, and stability, and radiographic diagnosed OA (K&L) and found a moderate agreement ( $k=0.57$ ). They found that knee pain (according to VAS) and stiffness (according to The Western Ontario and McMaster (WOMAC) Osteoarthritis Index) were the most important factors associated with radiographic knee OA. To our knowledge, no validated methods exist for defining symptomatic radiographic knee OA. The ACR criteria have been suggested to reflect a more severe stage of the disease<sup>144</sup>, therefore asking the patients about knee pain during a period of time, for instance on most days or the last 4 weeks, may be as valid as the ACR criteria<sup>144, 168</sup>.

## Results

The systematic review (Paper I) showed that long term follow-up studies on subjects with ACL injury were heterogeneous in terms of study participants, assessment methods, and low follow-up rates. Thus, stating conclusions on the prevalence of knee OA was difficult in this population. After performing a grading of the studies with respect to methodological quality, the high quality studies showed a prevalence of OA for isolated ACL injury of 0-13% and a prevalence of OA for combined injuries of 21-48%. As additional meniscal or chondral injuries have shown to be of the most important risk factors for development of knee OA, future studies should continue to group the ACL population in isolated and combined injuries to provide more accurate results on knee OA. We detected a prevalence of radiographic knee OA of 80% for those with additional meniscal injury and 62% for those with isolated ACL injury (Paper II). These numbers seems very high compared to the high quality studies examined in the systematic review (Paper I)(0-13% versus 21-48%). However, 34 of the 43 subjects (84%) with OA in the isolated group had mild OA (K&L grade 2), and for those with combined injury had 48 of 90 mild OA (53%) including emphasis of osteophytes (Paper II). If we compare the results for only K&L grade 3 and 4 (including also definite JSN) in Paper II with the results in the systematic review (Paper I), we find more comparable results. The prevalence of knee OA for isolated injuries was 10% (Paper II) and in the systematic review 0-13%, and our results for combined injuries showed a prevalence of OA of 37% and in the systematic review 21-48%. Weaknesses with and differences between the radiological classifications methods may explain the different numbers detected in the studies. Schiphof et al.<sup>172</sup> reviewed different classification criteria for OA,

and found that intrarater reliabilities for radiographic classification systems were overall good ( $k=0.79-0.94$ ), however, the interrater results were poorer ( $k=0.57-0.94$ ). The authors suggested separated lesion scoring or overall scoring using K&L classification to define knee OA. In addition, they suggested examination of knee pain. A consensus on radiographic methods is needed to be able to state true knowledge on the prevalence of knee OA in the ACL injured population. As the K&L classification define mild knee OA with osteophytes and possible JSN, a patient will be diagnosed with knee OA if a definite osteophyte is present, but without definite JSN. The IKDC classification system define knee OA based on reduced JSW, thus, the comparisons across studies may mislead the results on the prevalence of knee OA. The high prevalence of radiographic knee OA detected in the present study (Paper II) may thus be explained by emphasizing different radiographic findings than in the high quality studies (Paper I). Evaluation of symptomatic radiographic knee OA was only performed in one of the studies included in the systematic review<sup>115</sup>. Symptomatic radiographic knee OA should be more emphasized in the literature on ACL reconstructed subjects to better identify those who need treatment.

The prospective knee function outcomes significantly improved from 6 months to 10-15 years after the ACL reconstruction (Paper II). With a Cincinnati knee score above 80, muscle strength indexes above 90%, and hop test indexes above 90%, knee function can be considered satisfactory 10-15 years after ACL reconstruction (Paper II)<sup>120, 159</sup>. These results are in line with previous literature<sup>3, 102, 114</sup>. No differences between isolated compared to combined ACL and meniscal injuries and/or chondral lesions were detected for knee function over time. As meniscal injuries may be asymptomatic, the lack of significant differences in knee function outcomes between the groups may be reasonable. The absolute muscle strength values (J) significantly decreased from 2 years to 10-15 years after ACL reconstruction for the injured knee and for hamstrings strength for the contralateral knee. As shown in Table 3, Paper II, the absolute quadriceps strength values at 60°/sec significantly decreased with 5% from 2 to 10-15 years for those with isolated ACL injury, and with 10% for those with combined injury. Decreased muscle strength is expected over time<sup>50</sup>, unless individuals are very active in sports or training<sup>8</sup>. A decrease in muscle strength of 5-10% between the age groups 20-29 and 30-39 has been shown in normative data<sup>50</sup>. The knee joint laxity showed no difference between the groups. The knee joint laxity significantly increased between the 6 month

and the 2 year follow-up for the combined injury group (Paper II) as has also been shown in other prospective studies<sup>32</sup>.

Already in 1966 Lawrence et al.<sup>106</sup> found a weak association between symptoms and radiographic knee OA in a population-based study from North of England, but a significant correlation between OA severity and symptoms were detected. From then until now, there has been a lack of agreement in the literature regarding the association between radiographic knee OA and knee symptoms reported by the patients. However, data from the present study (Paper III) showed in line with Lawrence et al. that radiographic severity plays an important role in the association between radiographic defined knee OA and knee symptoms, but also for knee function. There are two issues related to these findings: first, the literature should include radiographic severity when evaluating the association between radiographic knee OA and pain or symptoms. Second, according to our results on significant and clinically important differences in knee function for those with severe radiographic OA, there should be more focus on radiographic progression in this population. Our cohort showed 47% mild OA (K&L grade 2), but no associations with pain and impaired function in ADL and sports (KOOS subscales) were found for those with mild or moderate OA. However, their radiographic OA may progress over time along with an onset and progression of symptoms and impaired knee function. The lack of association between radiographic OA and symptoms in some studies may therefore be explained by the lack of analyses including radiographic severity. Bedson et al.<sup>22</sup> systematically reviewed the literature regarding the discrepancy between radiographic findings and function and symptoms. They concluded that the discrepancy between symptoms and radiographic findings seemed to be most obvious for mild radiographic changes. However, they found that severe radiographic changes, involving severe osteophyte formation, JSN, sclerosis, and deformity of bone ends as described for grade 4 of the K&L classification, correlated with increased symptoms and impaired knee function. Based on current evidence including this thesis on the significant association between severe radiographic knee OA and symptoms and function, future studies should include radiographic severity and not use the traditional cutoff (K&L  $\geq 2$ ) when studying the association between radiographic knee OA and symptoms and function.

The high prevalence of knee OA (Papers I and II), and the significantly and clinically important increased symptoms and impaired knee function seen for those with

severe radiographic OA (Paper III), led us to the importance of defining risk factors for radiographic knee OA as well as for symptomatic radiographic knee OA (Paper IV). The studies included in the systematic review reported several risk factors for development of knee OA, but few of the studies performed risk factor analysis with prospective data including regression models<sup>99, 148, 170</sup>. Increased age and meniscal injury at the time of ACL reconstruction are well documented risk factors for knee OA as also confirmed by the data in the present study (Paper I and Paper IV). The menisci work as shock absorbers in the knee joint and injury or resection of the meniscus have been frequently associated with knee OA<sup>58</sup>.

None of the studies included in the systematic review (Paper I) evaluated quadriceps weakness as a possible risk factor for development of knee OA. Despite the fact that quadriceps strength deficits are frequently seen after ACL injuries, there seem to be more focus on quadriceps weakness as a possible risk factor for knee OA in the rheumatologic literature<sup>174-176, 182, 183</sup>. According to the results in Paper IV, we detected no significant association between radiographic or symptomatic radiographic knee OA and quadriceps strength as measured at 6 months, 1 year, and 2 years post-operatively. We measured quadriceps strength both as absolute values, absolute values related to body weight, and as index values. The results are in line with other recently published studies<sup>97, 175</sup>. However, our data detected a significant association between symptomatic radiographic knee OA and loss of quadriceps strength between 2 years and 10-15 years postoperatively. As this association was not shown for radiographic knee OA, it was most likely an association with the knee pain only. By re-doing the same analysis for knee pain and loss of quadriceps strength, the association was shown to be stronger than for symptomatic radiographic OA (OR 1.03, 95% CI 1.01-1.06). The same pattern was also seen for the association between knee pain and the Cincinnati knee score at 2 years postoperatively. On the basis of our data, quadriceps weakness seems more likely to be a consequence of knee pain rather than a risk factor for radiographic OA. The predictors detected for symptomatic radiographic knee OA included also impaired self-reported knee function 2 years postoperatively. The same results were not shown for radiographic knee OA. Thus, those with symptomatic radiographic knee OA seem to have more symptoms or pain already 2 years postoperatively compared to those without symptomatic radiographic knee OA. Furthermore, recent studies have

suggested that hip strength may be associated with different aspects of knee OA<sup>25, 195</sup>, therefore, more attention should be given hip muscle strength in risk factor analyses.

Several possible risk factors remained unanswered based on this thesis (Paper I and Paper IV) such as ACL surgery, activity level, or malalignment. ACL surgery in itself is suggested as a predisposing factor for knee OA<sup>49, 113</sup>, as subjects with ACL reconstruction has shown to develop significantly more knee OA than those with nonoperative treatment<sup>99, 133</sup>. There was only one RCT included in the systematic review comparing primary repair of the ACL and nonoperative treatment<sup>125</sup>. This study detected no significant differences between the treatment methods, but primary repair of the ACL can not be compared to today's surgical procedures. The high prevalence of radiographic knee OA in the present study supported the hypothesis that an ACL reconstruction in itself not seem to prevent OA. In addition, few studies have evaluated activity level as a risk factor for knee OA, but two studies evaluated soccer players and found high prevalence of knee OA more than 10 years after the injury<sup>115, 205</sup>. Type of activity following the ACL reconstruction should be evaluated as a possible risk factor in future studies. Malalignment may be genetically based, or result from traumatic factors and lead to altered loading in the knee joint<sup>190</sup>. Tanamas et al.<sup>190</sup> found in a systematic review that there is not enough evidence to state if malalignment is a risk factor for incident radiographic knee OA, but malalignment seems to be a risk factor for progression of radiographic knee OA. Finally, obesity has been shown to be one of the most important risk factors for development of knee OA<sup>198</sup>. The ACL reconstructed population is likely to be more active than a population based sample, thus representing different populations. Our results (Paper IV) detected no significant association between BMI and either radiographic or symptomatic radiographic OA.

Current literature emphasizes that OA is a mechanical disease, with factors such as knee malalignment, meniscus lesions, ACL injuries, occupational loads and obesity as the most important risk factors for knee OA<sup>57</sup>. However, on the basis of our results, the literature may be clearer in the discussion of risk factors on the structural disease and the symptomatic disease.

## Conclusions

In this thesis the prevalence of knee OA and the development of knee function after ACL reconstruction have been explored. The results provided a comprehensive examination of the existing literature regarding long term follow-up studies on subjects who have suffered an ACL injury or have undergone ACL reconstruction. The study adds new knowledge with respect to long term prevalence of knee OA and knee function outcomes, the association between radiographic OA, knee symptoms, and function, and risk factors for both radiographic as well as symptomatic radiographic OA. The following conclusions can be drawn:

- I. The overall prevalence of radiographic knee OA 10-15 years after ACL reconstruction was 74% ( $K\&L \geq 2$ ), including 47% mild OA ( $K\&L$  grade 2)(Paper II). The prevalence of knee OA was significantly lower in individuals with isolated ACL injury (Paper I: 0-13%, Paper II: 62%) than in subjects with combined ACL and meniscal injury (Paper I: 21-48%, Paper II: 80%). The prevalence of knee OA including definite JSN ( $K\&L$  grade 3 and 4), was 10% for those with isolated injury and 37% for those with combined injury. Symptomatic radiographic OA was detected in 41% of the subjects, with no significant group differences (combined injury 46% and isolated injury 32%)(Paper II).
- II. Significantly improved knee function was detected from 6 months to 10-15 years after ACL reconstruction. No significant differences in self-reported knee function, clinical tests, or performance based tests were detected over time between subjects with isolated ACL injury compared to combined ACL with meniscal injury and/or chondral lesion (Paper II). Significantly decreased absolute muscle strength values were detected from 2 years to 10-15 years postoperatively.
- III. There were no significant associations between radiographic knee OA ( $K\&L \geq 2$ ) and knee pain, function, or QOL, except for symptoms 10-15 years after ACL reconstruction. Subjects with severe radiographic knee OA ( $K\&L$  grade 4) had

significantly impaired knee function, increased symptoms, and reduced QOL compared to ACL injured subjects without knee OA (Paper III).

- IV. Additional meniscal injury was the most important risk factor for radiographic OA in individuals with ACL injury (Paper I and Paper IV). Also individuals with increased age at the time of ACL reconstruction had significantly higher risk for radiographic OA (Paper IV). Low self-reported knee function 2 years postoperatively, and loss of quadriceps strength between 2 years and 10-15 years postoperatively were significantly associated with symptomatic radiographic knee OA (Paper IV).



## Clinical implications

- Loss of quadriceps strength after ACL reconstruction is associated with symptomatic radiographic OA, and in particular knee pain. Thus, it is important to focus on quadriceps strength in a longer time perspective than the usual 6-9 months rehabilitation period in subjects that have undergone ACL reconstruction. It is therefore of clinical importance to systematically test the muscle strength before the rehabilitation is finished, and furthermore to inform the patients on the value of maintaining strength for prevention of future knee pain.
- Impaired self-reported knee function 2 years after ACL reconstruction seems to predict symptomatic radiographic knee OA 10 years later. Systematic measurement of self-reported knee function may be valuable for the therapists to predict future knee function, but also important to target specific factors which are not fully rehabilitated.

## **Future perspectives**

- Studies with prospective examination of knee OA and longer follow-up period than 10-15 years are needed to be able to evaluate progression of radiographic knee OA.
- A universal validated method for measurement of symptomatic radiographic knee OA, including new imaging techniques, should be explored and made valuable for researchers as well as clinicians.
- Universal agreement on radiographic knee OA is needed.
- A RCT on long term outcomes between non-surgical treatment versus ACL reconstruction is needed.
- Risk factor studies should incorporate prospective evaluation of knee OA and several important risk factors, including prospective evaluation of muscle strength and activity level.
- More studies which aim to investigate preventive strategies of meniscal injuries as well as treatment and rehabilitation procedures for those with meniscal injuries are needed.
- Studies aiming at examine preventive efforts against ACL and meniscus injuries should continue to be an important research area in the future.

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## Papers I-IV













# **Knee function and prevalence of knee osteoarthritis after anterior cruciate ligament reconstruction. A prospective study with 10-15 years follow-up**

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## Abstract

**Background:** Few prospective long term studies of more than 10 years have reported changes in knee function and radiological outcomes after anterior cruciate ligament (ACL) reconstruction.

**Purpose:** To examine changes in knee function from 6 month to 10-15 years after ACL reconstruction, and to compare knee function outcomes over time for subjects with isolated ACL injury to those with combined ACL and meniscal injury and/or chondral lesion and/or medial collateral ligament (MCL) injury. Furthermore, the aim was to compare the prevalence of radiographic and symptomatic radiographic knee OA between subjects with isolated ACL injuries to those with combined ACL and meniscal and/or chondral lesions 10-15 years after ACL reconstruction.

**Study design:** Prospective cohort study.

**Methods:** Follow-up evaluations were performed on 221 subjects at 6 months, 1 year, 2 years, and 10-15 years after ACL reconstruction with bone-patellar-tendon-bone (BPTB) autograft. Outcome measurements were: KT-1000 arthrometer, Lachman and pivot shift tests, Cincinnati knee score, isokinetic muscle strength tests, hop tests, visual analogue scale (VAS) for pain, Tegner activity scale, and the Kellgren and Lawrence (K&L) classification.

**Results:** One hundred and eighty-one subjects (82%) were evaluated at the 10-15 year follow-up. A significant improvement over time was revealed for all prospective outcomes of knee function. No significant differences in knee function over time were detected between the isolated and combined injury groups. Subjects with combined injury had significantly higher prevalence of radiographic knee OA compared to those with isolated injury (80% and 62%) ( $p=.008$ ), but no significant group differences were shown for symptomatic radiographic knee OA (46% and 32%) ( $p=.053$ ).

**Conclusion:** An overall improvement in knee function outcomes was detected from 6 months to 10-15 years after ACL reconstruction for both individuals with isolated and combined ACL injury, but significantly higher prevalence of radiographic knee OA was found for individuals with combined injuries.

**Keywords:** ACL reconstruction, knee function, knee osteoarthritis, isolated and combined injury, long term follow-up

## INTRODUCTION

Anterior cruciate ligament (ACL) injuries are common in young athletic individuals. The treatment method often includes ACL reconstruction with the aim of restoring the mechanical stability of the knee joint and re-establishing knee function.<sup>52</sup> Studies have shown that subjects with ACL reconstruction have good clinical outcomes and knee function more than 10 years after surgery, however, few prospective studies have included evaluation of self-reported knee function, muscle strength, and hop tests over time for more than 10 years.<sup>2, 43, 27</sup> Furthermore, the reported prevalence of radiographic knee OA has varied from less than 10% to more than 90%.<sup>12, 14, 18, 27, 30, 54</sup> A recent systematic review by our group showed that studies with the highest methodological quality reported up to 13% radiographic tibiofemoral OA for isolated ACL injuries, and between 21% and 48% for subjects with combined ACL and meniscal injuries, more than 10 years after the injury.<sup>35</sup> The long term follow-up studies of subjects with ACL injuries in orthopaedic journals usually only report radiographic knee OA. However, symptomatic radiographic knee OA should also be studied.<sup>42</sup>

Several factors may influence the development of knee OA in individuals with ACL reconstruction. Meniscal tears with subsequent partial resections, as well as chondral lesions at the time of the ACL injury have shown to increase the prevalence of radiographic knee OA.<sup>29, 51</sup> However, less is known about the influence of additional injuries in patients with symptomatic radiographic OA. Despite the growing number of studies that have reported long term consequences of ACL injuries,<sup>23, 25, 28, 31, 32, 40, 55</sup> little knowledge exists on the long term functional and radiological outcomes for subgroups of subjects with isolated injuries compared to those with combined injuries. The existing studies are heterogeneous due to differences in study populations, treatment procedures, and radiological methods. In addition, a majority of the existing

studies have demonstrated methodological weaknesses, such as retrospective study design, small sample sizes, and high drop-out rates.<sup>35</sup> Thus, there is a need for prospective studies of subjects with ACL injuries that report functional and radiological outcomes. Therefore, the aim of the present study was to examine changes in knee function from 6 month to 10-15 years after ACL reconstruction, and to compare knee function over time for subjects with isolated ACL injury to those with combined ACL and meniscal injury and/or chondral lesion and/or medial collateral ligament (MCL) injury. Furthermore, the aim was to compare the prevalence of radiographic and symptomatic radiographic knee OA between subjects with isolated ACL injuries and those with combined ACL and meniscal and/or chondral lesions and/or MCL injury 10-15 years after ACL reconstruction.

## **MATERIALS AND METHODS**

Two hundred and twenty-one subjects scheduled for ACL reconstruction were included consecutively in studies from 1990 to 1997.<sup>7, 46, 47</sup> The inclusion criteria were: age between 15 and 50 years; isolated ACL injury or combined with meniscal injury, MCL injury, or chondral lesion. The exclusion criteria were: other major injuries to the lower extremities less than 1 year before surgery, and cruciate ligament injuries to the contralateral knee. Follow-up evaluations were performed at 6 months, 1 year, 2 years, and 10-15 years postoperatively.

Arthroscopy was used to verify all the ACL ruptures and chondral lesions, and the additional meniscal injuries up to 10-15 years. The subjects were asked at the 10-15 year follow-up if they had suffered any re-injuries after the ACL reconstruction, or if they had gone through any surgical procedures after the ACL reconstruction. Surgical files were collected for all subjects that reported re-injuries. The surgeon files for all the

included patients from the index operation and for re-injuries have thoroughly been read to extract data on additional injuries and ACL graft ruptures. The MCL injuries were diagnosed by clinical assessment before surgery.

The combined injury group presented in this study consisted of subjects with ACL injury and meniscal injury suffered at the time of ACL reconstruction or during follow-up, either isolated or in combination with chondral lesion, or MCL injury. Subjects with chondral lesion (grade III and IV) at the femur condyle or at the tibia plateau, but with no meniscal injury, were included in the combined injury group. The isolated injury group involved subjects with isolated ACL injury from the index operation to the 10-15 year follow-up, as well as those with MCL injury reported to be healed at the time of ACL reconstruction.

The study was approved by the Regional Ethical Committee and The Data Inspectorate in Norway. All subjects signed an informed written consent, and could withdraw from participation in the study at any time point.

### **Surgical method**

The subjects were reconstructed with bone-patellar-tendon-bone autograft (BPTB), either with mini-open or arthroscopic procedure.<sup>7</sup> The arthroscopic procedure has previously been described by Aune et al.<sup>7</sup>: A 10-mm BPTB graft was harvested and trimmed to pass through a 9-mm diameter cannula. A guide wire was drilled using a drill guide (Linvatec Corp., Largo, Florida) from the medial side of the tibial tubercle (45°) to the tibial shaft, and advanced to the preserved ligament stump in the posterior portion of the ACL footprint. A femoral aimer with 7-mm offset (Linvatec Corp., Largo, Florida) was used (with the knee flexed) through the tibial tunnel and positioned at the 11-or 1-o'clock (right or left knee, respectively). The graft was fixed with 7×25-mm titanium

femoral and tibial interference screws (Linvatec Corp., Largo, Florida) and tensioned to 20 pounds while the knee was cycled to allow stress relaxation.<sup>7</sup> Meniscal tears were treated with partial meniscectomy, or sutured, or left untreated. The MCL injuries were sutured (grade III) or left surgically untreated (grade I and II). No treatment of the chondral lesions were performed except for shaving or removing loose edges.

### **Rehabilitation**

A rehabilitation program was included for all the subjects and described in previously published studies.<sup>7, 47, 48</sup> Rehabilitation exercises involved: stationary bicycling and exercises with partial weight-bearing (2-6 weeks postoperatively); exercises with full weight-bearing, functional activities, muscle strength and neuromuscular training (6-9 weeks post-operatively), and muscle strength and neuromuscular training, and running after 9 weeks postoperatively.<sup>7, 47, 48</sup>

### **Assessments**

The KT-1000 arthrometer (MEDmetric Corp., San Diego, California) using the manual maximum force test was included at all follow-ups to test anterior-posterior displacement of the tibia relative to the femur. The Lachman test<sup>15</sup> and the pivot shift test<sup>26</sup> were included at the 10-15 year follow-up. Weight was measured on all the follow-ups and body mass index (BMI) was calculated ( $\text{kg}/\text{m}^2$ ).

The Cincinnati knee score (6-100 points) was used to evaluate knee function at all follow-ups.<sup>34,8</sup> The questionnaire evaluates pain, swelling, giving way, general activity level, walking, stair climbing, running, jumping, and pivoting activities, and has previously been validated and used in other outcome studies.<sup>44, 46</sup> A score of 100 represents normal knee function.

Muscle strength tests were performed using the Cybex 6000 (Cybex Lumex Inc, Ronkonkoma, NY, USA) at all follow-ups. Isokinetic concentric knee flexion (hamstrings muscle strength) and extension (quadriceps muscle strength) were tested in a range from 0 to 90 degrees of knee flexion at 60 °/sec and 240 °/sec with respectively 5 and 30 repetitions. Total work (TW) in Joule (J) and index in percent [(injured/uninjured) x 100] were recorded.

The triple jump test for distance and the stair hop test previously tested for reliability and validity by our group, were performed at all follow-ups and reported as index [(injured/uninjured) x 100].<sup>33, 45</sup>

A visual analogue scale (VAS)<sup>41</sup> was used to measure knee pain at rest and during or right after physical activities at the 10-15 year follow-up. The subjects made a mark on a 10 cm line from no pain (0) to worst pain (10). Data on return to sports after the ACL reconstruction was collected by asking the subjects at the 10-15 year follow-up: “Did you return to sport after the ACL reconstruction?” We did not collect data on time of return to sports. The Tegner activity scale was included at the 10-15 year follow-up.<sup>53</sup>

Subjects with bilateral injuries suffered during follow-up were excluded from the analyses for knee joint laxity tests, the Cincinnati knee score, the muscle strength tests, and hop tests for all assessments.

Radiographs were included at the 10-15 year follow-up using the SynaFlexer frame (Synarc, Inc, Copenhagen, Denmark) to examine radiographic tibiofemoral knee OA. This frame placed the knees in approximately 20° of flexion and the feet positioned in 5° of external rotation. A 10° caudal x-ray beam ensured alignment of the beam corresponding to the medial tibial plateau.<sup>24</sup> The radiographs were taken bilaterally from a posteroanterior view. The radiographs were read according to the Kellgren and Lawrence (K&L) classification<sup>1, 21</sup>, including grade 0: no changes, grade 1: doubtful



narrowing of the joint space and possible osteophytic lipping, grade 2: definite osteophytes and possible narrowing of the joint space, grade 3: moderate multiple osteophytes, definite narrowing of the joint space, and some sclerosis, and possible deformity of the bone ends, grade 4: large osteophytes, marked narrowing of the joint space, severe sclerosis and definite deformity of the bone ends. Grade  $\geq 2$  was used to define OA.<sup>50</sup>

A question developed for estimating the prevalence of symptomatic knee OA was included<sup>49</sup>: “During the past 4 weeks, have you had knee pain in the injured knee?” Those who answered yes to this question combined with K&L grade  $\geq 2$  was considered to have symptomatic radiographic knee OA.<sup>38</sup>

All the radiographs were read by one radiologist. We included intra-rater reliability tests for the radiologist with at least a four week interval. Inter-rater reliability test was also performed including the radiologist and one orthopaedic surgeon on 35 radiographs for both knees (n=70), with functional and self-administered outcomes unknown to the readers. Blinding of the reconstructed knee on the x-rays was not possible, due to the visible screws in the surgically treated knee.

### **Statistical methods**

Statistical Package for Social Sciences (SPSS 16.0, SPSS Inc, Chicago, Illinois) was used for all statistical analyses. All variables were tested for normality using the Kolmogorov-Smirnov test. Analysis of variance (ANOVA) (mixed between-within subject model) and Bonferroni post hoc test were used to test changes over time between and within groups for all the prospective outcome measurements. The Friedman test was used to measure changes between specific time points for the Cincinnati knee score. Student's t-tests were used for group comparisons when normality was accepted (age, BMI, time

between injury and surgery) and Mann-Whitney U test was used when normality was rejected (VAS, Tegner). Chi-square test was used for group comparisons of two categorical variables (differences in gender, return to sports, and OA for the isolated and combined groups, respectively). Kappa statistic was performed to determine intra-rater and inter-rater reliability of the reading of the radiographs. A p-value of <.05 was considered statistical significant.

## **RESULTS**

One hundred and eighty-one subjects (82%) consented to participate at the 10-15 year follow-up, with a mean follow-up time of 12.4 ( $\pm 1.2$  years) (Figure 1). Subject characteristics are presented in Table 1. The activities performed at the time of injury were team handball, soccer or basketball (61%), alpine skiing (21%), and other physical activities (12%). Activity data at the time of injury were missing for eleven subjects (6%). One hundred and twenty-one subjects (67%) returned to sport after the rehabilitation period was finished: 50 subjects returned to soccer (28%), 25 subjects to team handball (14%), 8 subjects returned to basket ball (4%), 9 returned to other ball sports (5%), 22 returned to alpine skiing (12%), and 7 returned to other sport activities (4%). No significant differences between the isolated and combined groups were detected for those who returned to sport or not, or type of return to sport activities.

Thirty-seven subjects (20%) were injured in the contralateral knee during the follow-up: 15 isolated ACL injuries (8%), 11 combined ACL and meniscal injuries (6%), and 11 meniscal injuries (6%).

### **Additional injuries**

Isolated injuries were detected in 69 subjects (38%) and combined injuries were detected in 112 subjects (62%) (Table 2). Eight of the 106 subjects (7%) suffered meniscal injuries during the follow-up period. A total of 127 partial meniscal meniscectomies were performed in 106 subjects: 28 (22%) before; 69 (54%) during, and 30 (24%) after the ACL reconstruction. Meniscal sutures were performed in 8 subjects (8%), and no meniscal treatment in 8 subjects (8%). Chondral lesions at the time of surgery were reported in 37 subjects (20%). Nine subjects (3%) had full-thickness chondral lesions localized at femur (n=5); at femur and tibia (n=2), or at patella (n=2). One of the 37 subjects had superficial chondral lesion at the patella, but no meniscal injury, and was therefore included in the isolated injury group. Nine subjects suffered a MCL injury in whom 4 were sutured, and 5 were not surgically treated. According to the surgical files, 2 of the subjects had a healed MCL injury at the time of the ACL reconstruction, and were therefore included in the isolated group. Shaving of chondral lesions and removing loose edges were performed in 7 subjects (4%). Other surgical procedures performed during the follow-up included: osteotomy (n=1), removed scar tissue (n=12), removed screws (n=3), and arthroscopies (n=14).

Fifteen subjects (8%) had an ACL graft re-injury during the follow-up; 9 isolated ACL graft ruptures, 2 ACL graft ruptures combined with meniscal injury, and 4 partial ACL graft ruptures. One subject suffered a second ACL graft rupture. All the ACL graft ruptures were reconstructed. The mean time from the ACL reconstruction to re-operations of the ACL graft ruptures or meniscal injuries was  $57 \pm 47$  months.

### **Knee function outcomes**

A significantly increased knee joint laxity (KT-1000 manual maximum test) was revealed from 6 months to 10-15 years for the whole cohort ( $p<.001$ ). But there were no significant differences in knee joint laxity (KT-1000) over time for the subjects with isolated injuries (Table 3). No significant differences for the Lachman or Pivot shift tests were found for the isolated and combined injury groups (Table 4).

A significantly improved Cincinnati knee score was detected from 6 months to 10-15 years for the whole cohort ( $p<.001$ ). No significant group differences were shown over time (Table 3; Figure 2).

A significant improvement in quadriceps and hamstrings muscle strength (J and %) and hop tests (%) was detected over time for all the measurements, but no group differences were found (Table 3; Figure 3 and 4).

No significant differences were found between the groups for VAS pain at rest (isolated group:  $0.5\pm0.9$  and combined group:  $0.8\pm1.5$ ), or pain during activity (isolated group:  $1.5\pm1.8$  and combined group:  $2.1\pm2.2$ ) at the 10-15 year follow-up.

### **Radiological outcome**

Radiographs were performed on 181 subjects 10-15 years after ACL reconstruction (Table 5). K&L grade  $\geq 2$  was detected in 74% of the subjects ( $n=133$ ), including 47% grade 2. Symptomatic radiographic knee OA was revealed in 41% of the subjects ( $n=74$ ). The combined injury group revealed significantly higher prevalence of radiographic knee OA compared to the isolated injury group (80% and 62%) ( $p=.008$ ), but no significant group differences were detected between isolated injury group ( $n=22$ ) compared to combined injury group ( $n=52$ ) for symptomatic radiographic OA (46% and 32%) ( $p=.053$ ). Seven of the 9 subjects with full-thickness chondral lesions at the time of

surgery had K&L grade 3 or 4. Six of the 9 subjects with full-thickness chondral lesions had symptomatic radiographic knee OA. The intra-rater and inter-rater reliability tests revealed a Kappa of 0.77 and 0.57, respectively.

## DISCUSSION

Significantly improved knee function was detected from 6 months to 10-15 years in individuals with isolated and combined ACL injury. No significant differences in knee function over time were detected between the isolated and the combined injury group. But subjects with combined injuries revealed a significantly higher prevalence of radiographic knee OA than those with isolated ACL injuries (80% and 62%) ( $p=.008$ ). A similar trend was shown for symptomatic radiographic knee OA, but the result was not significant (46% and 32%) ( $p=.053$ ).

Normal, or nearly normal knee joint laxity (grade 0 and 1) were found in over 80%, 10-15 years after ACL reconstruction. These results corresponded to the results of previous long term follow-up studies of ACL injured subjects.<sup>16, 25, 40</sup> The Cincinnati knee scores showed improved mean scores over time, but no significant group differences were revealed. To our knowledge, no other studies with more than 10 years follow-up on ACL reconstructed subjects have evaluated knee function over time using self-reported outcome such as the Cincinnati knee score. However, even though the mean scores over time was >80 points; more than 30% revealed mean values less than 80 points for both the isolated injury group and the combined injury group. This may indicate that a majority of the subjects revealed good knee function corresponding to normative data for other similar outcomes measures<sup>4, 6</sup>, but it also revealed that 30% of the subjects had impaired knee function over time.

The muscle strength deficits between the injured and uninjured knees were on average less than 10% both at the 2 year and the 10-15 year follow-up. Sixty percent of the subjects in the isolated group, but only 38% in the combined group showed quadriceps index values >90% at the 10-15 years follow-up. This indicated that more subjects with isolated injury had normal index values than those with combined injuries ( $p=0.012$ ). Ageberg et al.<sup>2</sup> reported isokinetic index values between 94-102%, 1 year, 3 years, and 15 years after ACL injury, and 77% showed index values above 90%.<sup>2</sup> The study by Ageberg et al. included non-surgically treated patients in whom 33% had additional meniscal injury, and they excluded subjects with re-injuries. Quadriceps weakness has been among the neuromuscular deficiencies seen after ACL injuries.<sup>37</sup> Our cohort showed significantly increased absolute muscle strength values from the 6 month to the 2 year follow-up, but decreased absolute muscle strength values from 2 years to 10-15 years. The significantly decreased absolute muscle strength values detected from 2 to 10-15 years may be explained by increased age<sup>39</sup> and reduced activity level. The median Tegner score of 4 at the 10-15 year follow-up, was lower compared to the median score of 6 reported for individuals with normal knees with a mean age of 41 years.<sup>11</sup> Other studies with more than 10 years follow-up have reported Tegner scores between 4 to 6.<sup>22, 30, 54, 57</sup> The differences in activity level reported in these studies may be due to different study populations. The reduced activity level compared to the normative data presented by Briggs et al.<sup>11</sup> revealed that subjects with knee injuries seem to modify their activity level. The reduced muscle strength seen at the 10-15 year follow-up may also be due to other factors associated with impaired muscle function such as arthrogenic muscle inhibition or activation failure.<sup>9</sup> Impaired muscle function has been seen in subjects who have undergone joint surgery, but also individuals with knee OA.<sup>9, 13</sup>

A high prevalence of radiographic knee OA (74%), particularly mild radiographic knee OA (47%) was detected in the present study. Long term follow-up studies by Lohmander et al.<sup>28</sup> and von Porat et al.<sup>55</sup> evaluating soccer players have also reported high prevalence of knee OA (69% and 59%, respectively) in subjects with ACL injuries combined with meniscal injuries. Lebel et al.<sup>25</sup> retrospectively examined 98 subjects with BPTB autograft, and found a prevalence of knee OA of 13.6% in subjects with isolated injuries and 21.5% for subjects with combined injuries.<sup>17</sup> Other prospective studies have found a low prevalence of radiographic knee OA (1%-11%) in subjects who have undergone ACL reconstruction.<sup>40,14</sup> The above mentioned studies are discussed in a systematic review by Øiestad et al.<sup>35</sup> (see in particular Appendix 2). The variation in the reported prevalence may be explained by different study designs, different ACL populations, or different surgical procedures. Our study population seemed to have more additional injuries (62%) compared to the above mentioned studies which may explain the higher prevalence of radiographic knee OA in our study. However, in our cohort, not only subjects with combined injury, but also subjects with isolated injuries revealed a high prevalence of radiographic knee OA compared to other studies.<sup>25, 40, 56</sup> Nevertheless, among those with isolated injuries, only 10% had moderate and none had severe radiographic knee OA (K&L grade 3 and 4). The corresponding numbers for the combined injury group were 27% with moderate and 10% with severe radiographic knee OA. Thus, the prevalence of moderate and severe radiographic OA was higher for those with combined injuries. Nevertheless, the ACL reconstruction did not seem to prevent the development of mild OA. More studies exploring non-operative treatment compared to reconstructive surgery are needed in order to detect and explain eventually differences in the prevalence of knee OA between these two treatment strategies.

The variation in reported radiographic knee OA may also as previously reported be explained by the use of different radiological classification systems.<sup>5, 19, 21, 35</sup> For instance, K&L grade 2 involves osteophytes and possible JSN, whereas both the IKDC classification and the Ahlbäck classification involve mainly JSN for defining knee OA. The K&L classification involves JSN as a criterion for grade 3 and 4, but not necessarily for grade 2. Thus, comparing results from studies that have included osteophytes to define knee OA to studies that have emphasized JSN to define knee OA may be cautiously done. If we compare results for K&L grade  $\geq 3$  to the IKDC grade  $\geq C$  and Ahlbäck grade  $\geq 1$ , our results on radiographic knee OA for subjects with isolated ACL injuries (10%) can be compared to the results by Lebel et al.<sup>25</sup> (13.6%). The corresponding numbers for combined injuries were 37% in our study and 21.5% in the study by Lebel et al.

Symptomatic radiographic knee OA was revealed in 41% of the subjects corresponding to a similar study reporting 46% symptomatic radiographic knee OA in soccer players.<sup>28</sup> Knee pain may be derived from other conditions than OA, for instance, anterior knee pain has been associated with the BPTB procedure.<sup>10</sup> The proportion of symptomatic OA may therefore have been overestimated.

The prevalence of radiographic knee OA in the uninjured contralateral knee was 15%, including 12% K&L grade 2 and 3% grade 3 in line the results from similar studies<sup>14, 28, 31, 54</sup> The contralateral knee is often used as control knee to avoid the costs of including a healthy control group, but may not be optimal due to also altered joint loading in the uninjured knee and previously reported neuromuscular bilateral alterations and cross-over effects seen after ACL injuries.<sup>3, 36</sup> However, by introducing the contralateral knees as a control group, perfectly matching of age, BMI, activity level, and genetic risk factors have been included.



The present study is the first to compare prospective long term data on knee function for subjects with isolated to those with combined injury. The study had a high follow-up rate (82%), and a relatively large study cohort compared to the existing literature.<sup>35</sup> However, some limitations need to be addressed: Radiographic evaluation was only performed at the 10-15 year follow-up, thus we have no data on the onset of knee OA. In addition, the inter-rater reliability data showed moderate results. The time span from the ACL injury to surgery showed a mean time of 28 month (range 0-278) giving a wide variation in time from the ACL injury to the 10-15 years follow-up. The retrospectively collected data on additional injuries may have underestimated the number of additional injuries. Furthermore, we had no prospective data on activity level or return to sport (only retrospectively collected). A recently published study by Keays et al.<sup>20</sup> found no significant association between type of postoperative sport and OA in subjects with ACL reconstruction, but this should be further explored in future prospective studies. Future studies should also assess the correlation between knee function and knee OA, and furthermore, explore risk factors for development of knee OA. Finally, these relative young retired athletes should be followed longer than 10-15 years to examine the consequences of the high prevalence of mild knee OA, but also to assess what characterize those subjects that function well and do not develop knee OA more than 10 years after ACL reconstruction.

## **CONCLUSION**

Individuals with ACL injury revealed a significantly improved knee function from 6 months to 10-15 years after ACL reconstruction, with no significant differences found between individuals with isolated compared to those with combined injury over time. Subjects with combined injuries had significantly higher prevalence of radiographic

knee OA compared to those with isolated ACL injuries 10-15 years after ACL reconstruction (80% and 62%), but no significant differences between groups for symptomatic radiographic knee OA was detected. This study showed that individuals with an ACL reconstruction seem to restore and maintain good, but not normal knee function in the majority of the individuals with isolated and combined injuries more than 10 years after the ACL reconstruction.

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**Table 1. Subject characteristics at the 10-15 year follow-up (n=181)**

| <b>Variables</b>                         | <b>All</b> | <b>Isolated</b> | <b>Combined</b> | <b>p-value</b> |
|--|------------|-----------------|-----------------|----------------|
| Age (years)                              | 39.5 (8.6) | 37.5 (8.2)      | 40.7 (8.7)      | .02            |
| Females, number (%)                      | 76 (43)    | 36 (47)         | 40 (53)         |                |
| Males, number (%)                        | 105 (57)   | 33 (31)         | 72 (69)         | .03            |
| Time between injury and surgery (months) | 28 (52)    | 7.1 (10.7)      | 42.4 (63)       | <.001          |
| VAS at rest (mm) (0-10)                  | 0.7 (1.3)  | 0.5 (0.9)       | 0.8 (1.5)       | .23            |
| VAS during or after activity (mm) (0-10) | 1.8 (2.1)  | 1.5 (1.8)       | 2.1 (2.2)       | .07            |
| Tegner, median (min-max) (0-10)          | 4 (1-9)    | 4 (1-9)         | 4 (1-9)         | .72            |

Values are given as mean (SD, standard deviation) unless otherwise stated; VAS, visual analogue scale.

**Table 2. Frequencies (%) of additional injuries at the 10-15 year follow-up**

| <b>Type of injury</b>                  | <b>All (n=181)</b> | <b>Unilateral injury (n=144)</b> |
|--|--------------------|----------------------------------|
| Isolated injury                        | 69 (38)            | 58 (40)                          |
| Medial meniscal tear                   | 38 (21)            | 28 (19)                          |
| Lateral meniscal tear                  | 20 (11)            | 16 (11)                          |
| Medial and lateral meniscal tears      | 14 (8)             | 13 (9)                           |
| MCL and meniscal tear                  | 4 (2)              | 2 (2)                            |
| Chondral lesion and meniscal tear      | 27 (15)            | 18 (13)                          |
| Chondral lesion, MCL and meniscal tear | 3 (2)              | 3 (2)                            |
| Chondral lesions                       | 6 (3)              | 6 (4)                            |

MCL, medial collateral ligament.



Table 3. Prospective outcomes from 6 months to 10-15 years (n=144)

| Variable                                 | Type of injury  | 6 months |      | 1 year |                   | 2 years |                    | 10-15 years |                     | Between group differences p-value |
|--|-----------------|----------|------|--------|-------------------|---------|--------------------|-------------|---------------------|-----------------------------------|
|  |                 | Mean     | ±SD  | Mean   | ±SD               | Mean    | ±SD                | Mean        | ±SD                 |                                   |
| Body mass index                          | Isolated (n=41) | 23.2     | ±3.2 | 23.1   | ±2.3              | 23.1    | ±2.3               | 25.2        | ±3.0 <sup>abc</sup> | 0.105                             |
|  | Combined (n=81) | 23.7     | ±3.1 | 23.8   | ±2.9              | 23.9    | ±3.0               | 26.8        | ±4.0 <sup>abc</sup> |                                   |
| KT-1000, Manual maximum (mm)             | Isolated (n=43) | 2.7      | ±2.8 | 3.1    | ±2.3              | 3.5     | ±2.4               | 2.8         | ±2.7                | 0.502                             |
|  | Combined (n=69) | 2.3      | ±2.9 | 2.7    | ±3.0              | 3.1     | ±3.1 <sup>a</sup>  | 2.7         | ±3.4                |                                   |
| Cincinnati knee score (6-100)            | Isolated (n=41) | 79       | ±12  | 85     | ±12 <sup>a</sup>  | 87      | ±12 <sup>ab</sup>  | 85          | ±15 <sup>a</sup>    | 0.169                             |
|  | Combined (n=69) | 77       | ±13  | 81     | ±13 <sup>a</sup>  | 85      | ±13 <sup>ab</sup>  | 82          | ±16 <sup>a</sup>    |                                   |
| Hamstrings muscle strength (J) (60°/sec) | Isolated (n=33) | 466      | ±151 | 531    | ±148 <sup>a</sup> | 535     | ±147 <sup>a</sup>  | 482         | ±149 <sup>bc</sup>  | 0.448                             |
|  | Combined (n=59) | 493      | ±166 | 561    | ±165 <sup>a</sup> | 580     | ±176 <sup>a</sup>  | 481         | ±172 <sup>bc</sup>  |                                   |
| Hamstrings muscle strength (J)(240°/sec) | Isolated (n=33) | 1386     | ±395 | 1449   | ±383              | 1470    | ±454               | 1321        | ±417 <sup>bc</sup>  | 0.733                             |
|  | Combined (n=58) | 1454     | ±555 | 1470   | ±543              | 1542    | ±577               | 1300        | ±492 <sup>abc</sup> |                                   |
| Quadriceps muscle strength (J) (60°/sec) | Isolated (n=33) | 594      | ±237 | 711    | ±234 <sup>a</sup> | 791     | ±234 <sup>ab</sup> | 749         | ±220 <sup>a</sup>   | 0.843                             |
|  | Combined (n=59) | 596      | ±219 | 736    | ±208 <sup>a</sup> | 815     | ±216 <sup>ab</sup> | 733         | ±223 <sup>ac</sup>  |                                   |
| Quadriceps muscle strength (J)(240°/sec) | Isolated (n=33) | 1796     | ±623 | 1988   | ±623 <sup>a</sup> | 2099    | ±662 <sup>a</sup>  | 2076        | ±603 <sup>a</sup>   | 0.580                             |
|  | Combined (n=59) | 1829     | ±672 | 2035   | ±632 <sup>a</sup> | 2237    | ±657 <sup>ab</sup> | 2154        | ±714 <sup>a</sup>   |                                   |
| Triple jump test (%)                     | Isolated (n=32) | 95       | ±6   | 95     | ±4                | 98      | ±3                 | 99          | ±5 <sup>ab</sup>    | 0.176                             |
|  | Combined (n=54) | 92       | ±6   | 95     | ±5 <sup>a</sup>   | 98      | ±4 <sup>ab</sup>   | 98          | ±14 <sup>a</sup>    |                                   |
| Stair hop test (%)                       | Isolated (n=28) | 82       | ±14  | 93     | ±16 <sup>a</sup>  | 96      | ±8 <sup>a</sup>    | 102         | ±16 <sup>a</sup>    | 0.665                             |
|  | Combined (n=50) | 82       | ±20  | 91     | ±11 <sup>a</sup>  | 94      | ±7 <sup>a</sup>    | 103         | ±15 <sup>abc</sup>  |                                   |

J, Joules; <sup>a</sup>Significantly different from 6 months; <sup>b</sup>Significantly different from 1 year; <sup>c</sup>Significantly different from 2 years (p<.05).

**Table 4. Knee joint laxity tests in subjects with unilateral ACL injury 10-15 years after ACL reconstruction (n=144)**

|             |          | Number | Grade 0 (%) | Grade 1 (%) | Grade 2 (%) | Grade 3 (%) |
|-------------|----------|--------|-------------|-------------|-------------|-------------|
| Lachman     | Isolated | 58     | 16 (28)     | 32 (55)     | 10 (17)     | 0 (0)       |
|             | Combined | 86     | 30 (35)     | 43 (50)     | 12 (14)     | 1 (1)       |
| Pivot shift | Isolated | 58     | 34 (59)     | 14 (24)     | 9 (16)      | 1 (1)       |
|             | Combined | 86     | 60 (70)     | 19 (22)     | 6 (7)       | 1 (1)       |

The side-to-side difference for the Lachman test was graded as either grade 0 (normal), grade 1 (<5 mm difference), grade 2 (6-10 mm difference), or grade 3 (>10 mm difference). The pivot shift test was graded as grade 0 (normal), grade 1+ ("slip"), grade 2+ ("jump"), and grade 3+ ("transient lock").

Table 5. Kellgren and Lawrence and knee pain scores given as frequencies (%) at the 10-15 year follow-up

| Score    | Injured<br>(n=181) | Uninjured<br>(n=181) | Injured<br>Isolated<br>injury<br>(n=69) | Injured<br>Combined<br>injury<br>(n=112) | Uninjured<br>Without<br>injury<br>(n=144) | Uninjured<br>With<br>injury<br>(n=37) | Uninjured<br>Isolated<br>injury*<br>(n=69) | Uninjured<br>Combined<br>injury*<br>(n=112) | Knee pain<br>(n=97/181) |
|----------|--------------------|----------------------|---|--|---|---------------------------------------|--|---|-------------------------|
| <b>0</b> | 15 (8)             | 98 (54)              | 10 (15)                                 | 5 (5)                                    | 92 (64)                                   | 7 (16)                                | 47 (68)                                    | 51 (46)                                     | 7 (4)                   |
| <b>1</b> | 33 (18)            | 38 (21)              | 16 (23)                                 | 17 (15)                                  | 31 (21)                                   | 6 (19)                                | 12 (17)                                    | 26 (23)                                     | 16 (9)                  |
| <b>2</b> | 84 (47)            | 31 (17)              | 36 (52)                                 | 48 (43)                                  | 17 (12)                                   | 14 (38)                               | 7 (10)                                     | 24 (21)                                     | 49 (27)                 |
| <b>3</b> | 38 (21)            | 11 (6)               | 7 (10)                                  | 31 (27)                                  | 4 (3)                                     | 7 (19)                                | 2 (3)                                      | 9 (8)                                       | 18 (10)                 |
| <b>4</b> | 11 (6)             | 3 (2)                | 0 (0)                                   | 11 (10)                                  | 0 (0)                                     | 3 (8)                                 | 1 (2)                                      | 2 (2)                                       | 7 (4)                   |

\*Isolated or combined injury in the target knee.

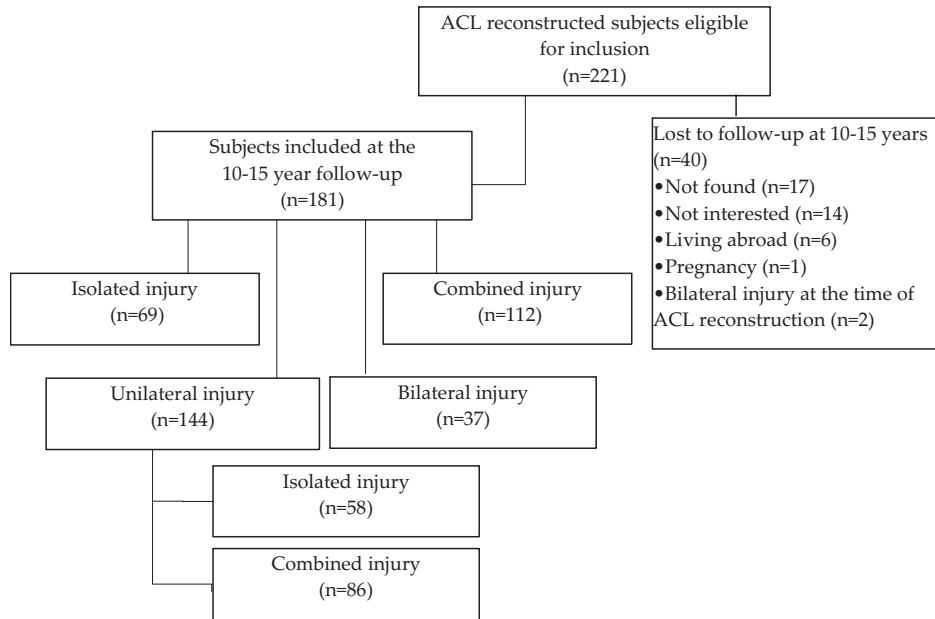


Figure 1. Flow-chart of the subjects included in the 10-15 year follow-up study

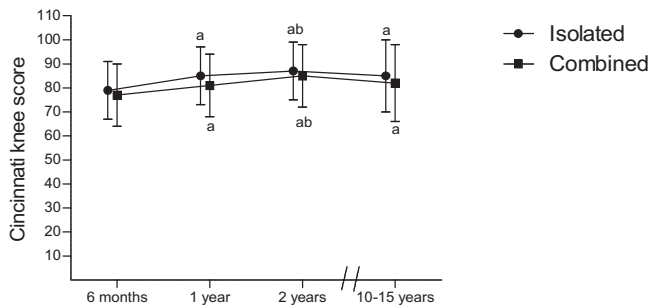


Figure 2. Cincinnati knee scores for the isolated and the combined injury groups at 6 months, 1 year, 2 years, and 10-15 years after ACL reconstruction. No group differences were detected over time. <sup>a</sup>Significantly different from 6 months; <sup>b</sup>Significantly different from 1 year ( $p < .05$ ).

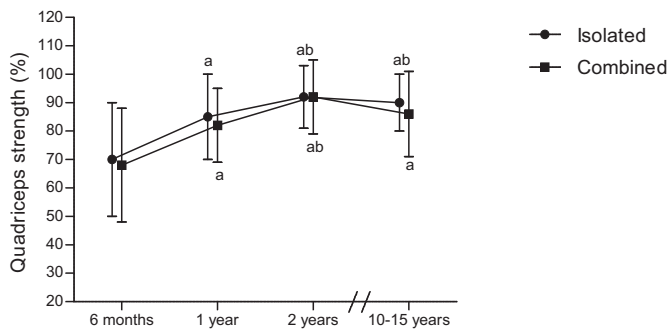


Figure 3. Quadriceps strength index given for the isolated group and the combined group at 6 months, 1 year, 2 years, and 10-15 years after ACL reconstruction. No group differences were detected over time. <sup>a</sup>Significantly different from 6 months; <sup>b</sup>Significantly different from 1 year ( $p < .05$ ).

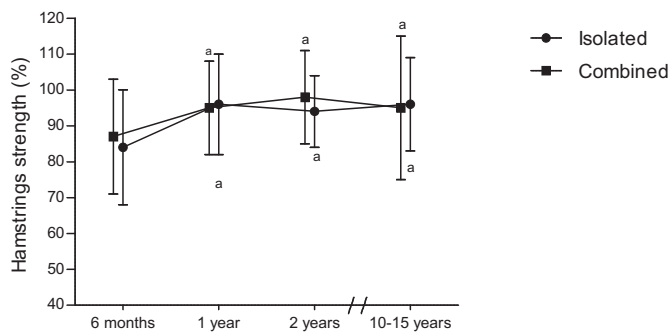


Figure 4. Hamstrings strength index given for the isolated and the combined injury groups at 6 months, 1 year, 2 years, and 10-15 years after ACL reconstruction. No group differences were detected over time. <sup>a</sup>Significantly different from 6 months ( $p < .05$ ).







# **The association between radiographic knee osteoarthritis and knee symptoms, function, and quality of life 10-15 years after anterior cruciate ligament reconstruction**

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## ABSTRACT

**Background:** There are conflicting results in the literature regarding the association between radiographic knee OA and symptoms and function in subjects with previous anterior cruciate ligament (ACL) reconstruction.

**Purpose:** To investigate the associations between radiographic tibiofemoral knee OA and knee pain, symptoms, function, and knee-related quality of life (QOL) 10-15 years after ACL reconstruction.

**Study design:** Cross-sectional study

**Material and methods:** Two hundred and fifty-eight subjects were consecutively included at the time of ACL reconstruction and followed-up prospectively. We included the Knee Injury and Osteoarthritis Outcome Score (KOOS) to evaluate knee pain, other symptoms (symptoms), activities of daily living (ADL) and sport and recreation (Sport/Rec), and QOL. The subjects underwent standing radiographs 10-15 years after the ACL reconstruction. The radiographs were graded with the Kellgren and Lawrence (K&L) classification (grade 0-4).

**Results:** Two hundred and ten subjects (81%) consented to participate at the 10-15 year follow-up. Radiographic knee OA (K&L  $\geq$  grade 2) was detected in 71%, and 24% showed moderate or severe radiographic knee OA (K&L grade 3 and 4). No significant associations were detected between radiographic knee OA (K&L grade  $\geq$ 2) and pain, function, or QOL, respectively, but subjects with radiographic knee OA showed significantly increased symptoms. Severe radiographic knee OA (K&L grade 4) was significantly associated with more pain, symptoms, impaired Sport/Rec, and reduced QOL.

**Conclusion:** Subjects with radiographic knee OA showed significantly more symptoms than those without OA, and subjects with severe radiographic knee OA had significantly

more pain, impaired function, and reduced quality of life than those without radiographic knee OA 10-15 years after ACL reconstruction.

## INTRODUCTION

Knee osteoarthritis (OA) is considered an important disease in the western world because it may cause knee pain and disability.[1] But in the orthopedic literature OA is usually defined solely based on radiographic abnormalities according to classification criteria defined in atlases.[2-6] In the rheumatologic literature, however, knee OA is defined by radiographic abnormalities in combination with pain or symptoms.[7,8] Bedson et al.[9] reviewed population based observational studies and reported that of subjects with knee pain, between 15-76% had radiographic knee OA.

The association between radiographic knee OA and knee pain, symptoms, or function has not been consistent,[10-12] with some studies reporting a weak association.[13] The cut off for defining radiographic knee OA usually includes abnormalities such as one osteophyte and possible joint space narrowing [Kellgren and Lawrence (K&L) grade 2], which is in the literature defined as the mildest grade of OA.[2] However, studying the association between pain or function and one osteophyte compared to the association between pain or function and *severe* radiographic findings, such as definite joint space narrowing, multiple osteophytes, sclerosis, and bone enlargements may give different results.[12] Neogi et al. [14] suggested that radiographic *severity* was strongly associated with knee pain. However, the association between severity of radiographic knee OA and knee pain, symptoms, or function is not thoroughly explored in subjects with previous ACL injury. Furthermore, increased age, female gender, and high BMI have been shown to be significant risk factors for knee OA[15], and also significantly associated with knee symptoms and function.[16] Few

studies, however, have adjusted for significant risk factors in the analyses of the association between radiographic findings and pain, symptoms, or function. This may cause conflicting results. Ideally, studies should include large populations to enable adjustments for potential confounding factors.

Knee injuries, including anterior cruciate ligament (ACL) ruptures and meniscal injuries, have been suggested as important risk factors for the development of knee OA.[17-19] Nevertheless, long term follow-up studies of more than 10 years after ACL injuries are rare, and there are few studies examining the association between radiographic knee OA and knee pain, other symptoms, function, or knee-related quality of life (QOL).[20] Furthermore, to our knowledge, no studies with more than 10 years follow-up after ACL reconstruction have examined the association between these variables and radiographic severity. Therefore, the aim of the present study was to investigate the association between radiographic tibiofemoral knee OA using the traditional cutoff for radiographic knee OA (K&L <2 vs. ≥2) and knee pain, symptoms, function, and QOL 10-15 years after ACL reconstruction. Furthermore, the aim was to examine the association between mild, moderate, and severe radiographic knee OA and knee pain, symptoms, function, and QOL, respectively.

## **MATERIALS AND METHODS**

Two hundred and fifty-eight subjects who underwent ACL reconstruction were consecutively included in studies between 1990 and 1997. The subjects were included if they were between 14 and 50 years, had isolated ACL injury or combined with meniscus injury, and/or chondral lesion, and/or medial collateral ligament (MCL) injury.[21-23] The exclusion criteria were injuries to the contralateral knee and fractures in both legs the last year before inclusion. The subjects were operated with bone-patellar-tendon-

bone (BPTB) autograft or hamstrings tendon (HT) autograft previously described by Aune et al.[21] The chondral lesions, the MCL injuries and the meniscal injuries suffered prior to or at the time of the ACL injury and the meniscal injuries suffered during the follow-up have retrospectively been extracted from surgeon files of all the subjects included at the 10-15 year follow-up. The MCL injuries were diagnosed by clinical assessment before the ACL reconstruction.

A supervised rehabilitation program was included postoperatively as a three phase program lasting for 6-9 months.[21,23] The subjects have been followed-up prospectively at 6 months, 1 year, 2 years,[21-23] and 10-15 years[24,25] postoperatively with functional and clinical assessments, but for the aim of this study only the 10-15 year follow-up evaluations were included.

The Regional Committee for Medical and Health Research Ethics in Norway has approved the study and the participants signed an informed consent prior to participating at the 10-15 year follow-up.

## **Assessments**

The Knee Injury and Osteoarthritis Outcome Score (KOOS) was used to assess knee pain, symptoms, function, and QOL at the long term follow-up.[26] KOOS is a self-administered questionnaire comprising 5 subscales on pain, other symptoms (symptoms), activities of daily living (ADL) and sport and recreation (Sport/Rec), and QOL. The KOOS subscales are organized into categories for each question which are transformed to a 0-100 scale. Zero indicates extreme knee problems and 100 represent no knee problems. KOOS was developed for short and long term follow-up studies and has been validated on several types of injuries to the knee such as ACL and meniscal injuries, and posttraumatic OA.[27,28] The Tegner activity scale was used to assess the

activity level.[29] To calculate body mass index (BMI), we used the formula weight (kg)/height(m)<sup>2</sup>.

All the subjects participating at the 10-15 year follow-up went through a radiological assessment of the tibiofemoral joint. The procedure included standing radiographs with the knees flexed in approximately 20° and the feet 5° externally rotated by using a Plexiglas frame (SynaFlexer Inc, Copenhagen, Denmark). The frame has been validated for measuring joint space width in patients with knee OA.[30] Radiographs were taken bilaterally from a posteroanterior view.

One radiologist analyzed the radiographs using the K&L classification system.[2,31] The following definitions for each grade were used: grade 0: no changes, grade 1: doubtful narrowing of the joint space and possible osteophytic lipping, grade 2 (mild): definite osteophytes and possible narrowing of the joint space, grade 3 (moderate): multiple osteophytes, definite narrowing of the joint space, and some sclerosis, and possible deformity of the bone ends, grade 4 (severe): large osteophytes, marked narrowing of the joint space, severe sclerosis and definite deformity of the bone ends.

The radiologist performed intra-rater reliability test for the reading of the radiographs. The intra-rater test was performed with at least 4 weeks interval on 35 radiographs of both knees (n=70). The intra-rater reliability result for the x-ray evaluation showed kappa=0.77.

## **Statistical methods**

We used linear regression to evaluate the association between radiographic tibiofemoral OA and the KOOS subscales pain, other symptoms, ADL, Sport/Rec, and QOL with adjustment for age, gender, and BMI (SPSS 16.0, SPSS Inc, Chicago, Illinois). First, we

evaluated the radiographic OA using a dichotomized radiographic variable: no OA (K&L 0/1 = reference category) vs. OA (K&L grade  $\geq 2$ ). Second, we evaluated radiographic OA severity in more detail by dichotomizing each K&L grade still using K&L grade 0/1 as the reference category: K&L grade 2 vs. 0/1, K&L grade 3 vs. 0/1, and K&L grade 4 vs. 0/1. Standardized beta values, standard errors, 95% confidence intervals (CI), and p-values were given for all regression analyses. We used the Mann Whitney U test for group comparisons of non-parametric data (Tegner), and kappa analysis to evaluate the reliability test of the x-ray scores. All tests were two-tailed and we considered a p-value of 0.05 or less as statistically significant.

**Table 1. Subject characteristics at the 10-15 year follow-up (n=210)**

| <b>Variables</b>                                     | <b>Mean<math>\pm</math> SD</b> |
|--|--------------------------------|
| Age  | 39.1 $\pm$ 8.7                 |
| BMI  | 26.3 $\pm$ 3.6                 |
| Time from injury to surgery (months)                 | 24.8 $\pm$ 48.7                |
| Time from injury to the 10-15 year follow-up (years) | 13.7 $\pm$ 4.4                 |
| KOOS pain  | 90 $\pm$ 14                    |
| KOOS other symptoms                                  | 86 $\pm$ 16                    |
| KOOS activities of daily living                      | 95 $\pm$ 10                    |
| KOOS sports and recreation                           | 77 $\pm$ 24                    |
| KOOS knee-related quality of life                    | 75 $\pm$ 22                    |
| Tegner*  | 4 (1-9)                        |

SD, standard deviation; BMI, body mass index; KOOS, Knee injury and Osteoarthritis Outcome Score; \*The Tegner activity scale is given as median (minimum-maximum).

## RESULTS

Two hundred and ten subjects participated in the study (81%), 90 females (43%) and 120 males (57%). Subject characteristics are presented in Table 1. Of the 210 subjects, 29 (14%) were operated with HT graft, and 181 (86%) with BPTB graft. Isolated ACL injury was detected in 82 subjects (39%) and 128 subjects (61%) had additional meniscal injury, MCL injury or chondral lesion, or a combination of these (Table 2).

Eleven subjects had chondral lesions grade 3 (n=5) and grade 4 (n=6). Only 10 (8%) of the total of 121 (100%) subjects with meniscal injuries suffered the meniscal injury during the follow-up period. A total of 137 partial meniscal resections (91%) and 13 sutures (9%) were performed in the 210 subjects either before the ACL reconstruction (22%), at the time of ACL reconstruction (53%), or during the follow-up period (25%). The activities performed at the time of injury comprised of pivoting sports in 129 subjects (61%), mainly handball (n=37, 18%), soccer (n=70, 33%), or basket ball (n=9, 4%), alpine skiing in 46 subjects (22%), and other activities or unknown activity in 23 subjects (11%) and 12 subjects (6%), respectively. No significant difference in median Tegner activity scale was shown between subjects with or without radiographic knee OA. Fourteen subjects (7%) suffered a graft rupture during the follow-up period, and four subjects (2%) suffered a partial graft rupture verified through arthroscopic procedures.

Forty-five subjects (21%) were injured in the contralateral knee during the follow-up period including isolated ACL injuries in 19 subjects (9%), ACL partial tear in 1 subject (0.5%), ACL in combination with meniscal injury in 11 subjects (5.5%), and isolated meniscal injury in 14 subjects (6%).

**Table 2. Additional injuries at the 10-15 year follow-up (n=210)**

| <b>Type of injury</b>              | <b>Number</b> | <b>%</b> |
|------------------------------------|---------------|----------|
| Isolated ACL injury                | 82            | 39       |
| Medial meniscus                    | 39            | 19       |
| Lateral meniscus                   | 19            | 9        |
| Menisci                            | 26            | 12       |
| Meniscus and MCL                   | 5             | 2        |
| Meniscus, MCL, and chondral lesion | 3             | 2        |
| Meniscus and chondral lesion       | 29            | 14       |
| Chondral lesion                    | 7             | 3        |

MCL, medial collateral ligament.



Seventy-one percent of the subjects had radiographic signs of knee OA according to K&L  $\geq$  grade 2 (Table 3). The corresponding number for the contralateral knee was 25%. Moderate or severe knee OA (K&L  $\geq 3$ ) was detected in 24% for the target knee and 6% for the contralateral knee, respectively.

**Table 3. Frequency (%) of the Kellgren and Lawrence (K&L) scores for involved and contralateral knee (n=210)**

| K&L | Involved knee |      | Contralateral knee |      |
|-----|---------------|------|--------------------|------|
| 0   | 19            | (9)  | 114                | (54) |
| 1   | 42            | (20) | 43                 | (21) |
| 2   | 98            | (47) | 39                 | (19) |
| 3   | 40            | (19) | 11                 | (5)  |
| 4   | 11            | (5)  | 3                  | (1)  |

Table 4 shows unadjusted and adjusted results for the association between each KOOS subscale and radiographic knee OA (K&L  $< 2$  vs.  $\geq 2$ ). No significant associations were detected, except for symptoms. The adjusted analysis indicated that subjects with radiographic knee OA at the level of K&L  $\geq$  grade 2 had on average approximately 6 points lower KOOS other symptoms scores than those without radiographic knee OA.

**Table 4. Multiple regression analyses of the association between the Knee injury and Osteoarthritis Outcome subscales and Kellgren and Lawrence (K&L) grade  $\geq 2$  vs. grade  $< 2$  (n=206)**

| Dependent variables       | K&L $< 2$ vs. $\geq 2$ | Beta | Standard Error | 95% CI      | P-value |
|---------------------------|------------------------|------|----------------|-------------|---------|
| Pain                      | Unadjusted             | -4.1 | 2.2            | -8.4, 0.1   | 0.06    |
|                           | Adjusted               | -2.6 | 2.3            | -7.2, 2.0   | 0.26    |
| Other symptoms            | Unadjusted             | -5.9 | 2.4            | -10.6, -1.3 | 0.01    |
|                           | Adjusted               | -5.7 | 2.5            | -10.7, -0.6 | 0.03    |
| Activities of daily lives | Unadjusted             | -1.6 | 1.6            | -4.7, 1.4   | 0.29    |
|                           | Adjusted               | 0.2  | 1.7            | -3.0, 3.5   | 0.89    |
| Sports and recreation     | Unadjusted             | -7.3 | 3.7            | -14.6, 0.0  | 0.05    |
|                           | Adjusted               | -4.6 | 3.9            | -12.4, 3.1  | 0.24    |
| Quality of life           | Unadjusted             | -2.7 | 3.4            | -9.3, 3.9   | 0.42    |
|                           | Adjusted               | -0.9 | 3.6            | -8.0, 6.2   | 0.80    |

CI, confidence interval. Adjusted for gender, age, and body mass index.

Figure 1 shows the mean values for the KOOS subscales for each K&L grade. No significant associations were detected between the KOOS subscales and mild or moderate radiographic knee OA adjusted for gender, age, and BMI (Table 5). Subjects with severe radiographic knee OA had significantly lower values for the KOOS subscales than those without OA.

**Table 5. Multiple regression analysis of the association between the KOOS subscales\* and the K&L grades**

| KOOS           | Number | K&L grades | Beta  | Standard Error | 95% CI      | p-value |
|----------------|--------|------------|-------|----------------|-------------|---------|
| Pain           | 97     | 2          | -0.6  | 2.0            | -4.5, 3.3   | 0.77    |
|                | 40     | 3          | 2.6   | 2.6            | -2.4, 7.8   | 0.30    |
|                | 11     | 4          | -14.3 | 4.3            | -22.9, -5.8 | 0.001   |
| Other Symptoms | 97     | 2          | -4.1  | 2.2            | -8.4, 0.2   | 0.06    |
|                | 40     | 3          | 3.9   | 2.9            | -1.7, 9.5   | 0.17    |
|                | 11     | 4          | -11.6 | 4.9            | -21.3, -2.1 | 0.02    |
| ADL            | 97     | 2          | -0.4  | 1.4            | -3.2, 2.4   | 0.80    |
|                | 40     | 3          | 3.4   | 1.8            | -0.2, 7.0   | 0.06    |
|                | 11     | 4          | -7.3  | 3.2            | -13.4, -1.1 | 0.02    |
| Sport/Rec      | 97     | 2          | -1.1  | 3.4            | -7.8, 5.5   | 0.74    |
|                | 40     | 3          | 3.2   | 4.4            | -5.4, 11.8  | 0.46    |
|                | 11     | 4          | -20.6 | 7.4            | -35.2, -6.0 | 0.006   |
| QOL            | 97     | 2          | 2.8   | 3.1            | -3.2, 8.9   | 0.36    |
|                | 40     | 3          | 1.2   | 4.0            | -6.6, 9.1   | 0.76    |
|                | 11     | 4          | -20.7 | 6.6            | -33.9, -7.5 | 0.002   |

KOOS, Knee injury and Osteoarthritis Outcome Score; K&L, Kellgren and Lawrence; CI, confidence interval; ADL, activities of daily living; Sport/Rec, function in sports and recreation; QOL, knee related quality of life.\*Adjusted for gender, age, and body mass index. K&L grade 0 and 1 constitute the reference category for the independent dichotomous variables (n=60).

## DISCUSSION

The results revealed that subjects with radiographic knee OA had significantly increased symptoms compared to those without radiographic OA. Furthermore, highly significant associations were detected between severe radiographic knee OA and pain, symptoms, ADL, Sport/Rec, and QOL. It has been suggested that a change of 8-10 KOOS points constitutes a clinical relevant difference.[27] However 10 points have been arbitrarily

set and we suspect that it is difficult to state a common number for a clinical important difference for the different KOOS subscales. Therefore, the significantly increased symptoms for those with mild OA (6 points in mean difference) may be of clinical importance compared to those without radiographic OA. The significantly increased pain, symptoms, and reduced function seen in individuals with ACL reconstruction may be explained by the radiographic abnormalities.

No previous long term studies including subjects with ACL reconstruction have evaluated the relationship between knee symptoms and function and radiographic knee OA using regression analysis. However, previous studies have evaluated the difference in mean values of the KOOS subscales between ACL injured subjects with and without knee OA.[32-35] Lohmander et al.[32] reported significant increased pain and symptoms in female soccer players with radiographic knee OA compared to those without radiographic knee OA 12 years after ACL injury in line with our results for symptoms. The mean values for the KOOS subscales were, however, generally lower than those reported in our study. For instance, those with radiographic knee OA had a mean value for pain of 70, compared to 84 in our study. Furthermore, their Sports/Rec and QOL values were 24 and 23 points lower than our results, showing that the female soccer players reported more complaints 12 years after ACL injury compared to our cohort of both males and females. Our results showed no significant differences between females and males for the KOOS subscales. The subjects in the study by Lohmander et al. were younger compared to our cohort. They were only female soccer players, they were treated either with ACL reconstruction or non-operatively, and the study assessed both patellofemoral and tibiofemoral OA. Inclusion of both patellofemoral and tibiofemoral OA has been shown to be more frequently associated with knee pain and impaired function.[12] In addition, a drop-out rate of 35% was reported in the study by

Lohmander et al. These differences may explain the more impaired function found in their study. Meunier et al.[33] reported significantly increased pain and symptoms, and impaired function in ADL and Sport/Rec in subjects with radiographic OA compared to those without radiographic OA on average 15 years after the ACL injury. The mean KOOS subscales scores reported in their study were more similar to those in the present study except for the lower values for Sport/Rec (62 vs. 75 points), and QOL (63 vs. 74 points). Meunier et al. included both subjects with ACL reconstruction and non-operative treatment and subjects with grade 1 radiographic changes were included in the OA group. Our unadjusted results on the association between the KOOS subscales and radiographic OA were not very different from those of Meunier et al. (pain:  $p=0.06$ ; symptoms:  $p=0.01$ ; Sport/Rec:  $p=0.05$ ). Furthermore, Neuman et al.[34] studied ACL injured subjects without reconstruction 15 years after the injury and they reported almost identical mean values for the KOOS subscales as found in the present study. These authors detected no significant differences between subjects with or without radiographic knee OA also in line with another follow-up study of male soccer players.[35]

The moderate inter-rater reliability results found for different radiological classification systems[5] may be another explanation for the differences in results across studies with respect to the association between radiographic knee OA and pain, symptoms, and function. The different classification systems emphasize to some extent either osteophytes or joint space narrowing which may influence the cutoff for radiographic knee OA.[2-4] Common for the above mentioned studies and the present study was the long term follow-up of ACL injured subjects (>10 years), but the studies included different radiological classification systems without attention towards radiographic severity. In the present study we performed regression analysis with

adjustment for gender, age, and BMI as these factors have been shown to influence both the mean KOOS subscale values or the K&L scores.[16,26,36,37] The adjustment for the potential confounding factors did influence the associations, particularly for pain and Sport/Rec.

Biological, psychological, and social factors have all been shown to influence pain.[38] For instance, psychological factors have been strongly associated with functional impairment and pain after adjustment for radiographic severity in patients with knee OA.[39] Consequently, the lack of association between radiographic knee OA defined by the traditional cutoff and pain or function may be due to a true weak association. Our adjusted analyses showed that there were significant associations between severe radiographic knee OA and all KOOS subscales. Consequently, the follow-up studies on subjects with ACL reconstruction should emphasize the self-reported knee pain, symptoms, including effusion, locking, range of motion, and stiffness, and function, in addition to severity of radiographic knee OA, more than the prevalence of radiographic knee OA defined with a cutoff.

Our results revealed that those with severe radiographic knee OA had significantly lower values on the KOOS subscales compared to those without OA. However, only 11 subjects had severe radiographic OA, and all these individuals had additional meniscal injury (n=6) or meniscal and chondral injury (n=5). The increased pain and symptoms, and the impaired function in these subjects may be due to the additional injuries and not the radiographic abnormalities. Meniscal injury has shown to be the most important risk factor for development of knee OA in subjects with ACL injury,[5] but also for those without ACL injury.[40] Therefore, it is difficult to explain the sources of the pain and symptoms in this population. The KOOS other symptoms subscale includes questions related to effusion, locking, range of motion, and stiffness.

These factors may be associated with the previous ACL reconstruction and the additional meniscal injuries.[41] In addition, we detected no significant associations between moderate radiographic knee OA involving multiple osteophytes, definite narrowing of the joint space, and some sclerosis, and the KOOS subscales. Brandt et al.[42] suggested that the synovium and subchondral bone are major sources of joint pain in patients with knee OA, but also that other joint structures, including the menisci and periarticular muscles, may contribute to the knee pain. Nevertheless, it may be reasonable that the increased pain and symptoms, and impaired function detected in our study were due to the severe radiographic changes, and not to the additional meniscal injuries suffered several years ago. However, whether the meniscal injuries or the radiographic abnormalities caused the increased pain and impaired function for those with severe radiographic OA cannot be stated on the basis of our data.

The present study has some limitations: A drop-out rate of 19% may have biased the results, but there were no significant differences in gender or age between the study participants and those who dropped out. No data on the patellofemoral joint was available for this study. There may be a risk of type 2 error in the analyses, therefore, there may be true differences between those with radiographic OA and those without detected with larger sample size.

This study revealed that only individuals with severe radiographic OA 10-15 years after ACL reconstruction had significantly increased pain and reduced function compared to those without knee OA. Future research should perform risk factor analyses to provide further evidence for treatment methods to reduce the development or delay the progression of radiographic knee OA, but also study treatment methods targeting reducing pain and symptoms and increasing function. Finally, future studies on subjects with ACL injury should include assessment of radiographic severity and the

definition of knee OA should involve both radiographic abnormalities and pain or symptoms.

## **CONCLUSION**

Subjects with radiographic knee OA had significantly increased symptoms compared to those without radiographic OA. Subjects with severe radiographic knee OA had also significantly more pain, impaired function and reduced quality of life compared to those without radiographic knee OA 10-15 years after ACL reconstruction.

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**What is already known on this topic**

A high prevalence of radiographic knee OA is reported for individuals with ACL reconstruction, but long term self-reported knee function has shown to be good. Conflicting evidence exist on the association between symptoms or function and radiographic knee OA.

**What this study adds**

This study provides analyses on the association between radiographic severity and knee symptoms and function. This study detected that subjects with *severe* radiographic knee OA had increased symptoms and impaired function compared to those without radiographic knee OA more than 10 years after ACL reconstruction.



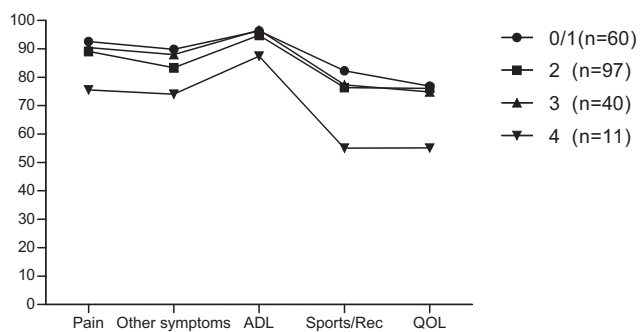
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**Figure 1.** Mean values for the subscales of the Knee injury and Osteoarthritis Outcome Score for each Kellgren and Lawrence grade (0-4)









# **Quadriceps muscle weakness after anterior cruciate ligament reconstruction: a risk factor for knee osteoarthritis?**

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## ABSTRACT

### Objectives

To identify risk factors for knee osteoarthritis (OA) 10-15 years after anterior cruciate ligament (ACL) reconstruction. We hypothesized that quadriceps muscle weakness after ACL reconstruction would be a risk factor for radiographic and symptomatic radiographic knee OA 10-15 years later.

### Methods

Subjects with ACL reconstruction (n=258) were followed for 10-15 years. Subjects with unilateral injury at the 10-15 year follow-up (FU) were included in the present study. Outcomes included the Cincinnati knee score, knee joint laxity, hop tests, and isokinetic muscle strength tests at 6 months, 1 year, and 2 years postoperatively. At the 10-15 year FU, radiographs were taken and graded according to the Kellgren and Lawrence classification (0-4).

### Results

Of the 210 subjects assessed at the 10-15 year FU (81%), 164 subjects had unilateral injury. The mean age ( $\pm$ SD) at ACL reconstruction was 27.4 ( $\pm$ 8.7) years. Increased age (OR 1.06, 95% CI 1.01, 1.11) and meniscal injury and/or chondral lesion (OR 2.05, 95% CI 1.00, 4.20) showed significantly higher odds for radiographic knee OA. Low self-reported knee function 2 years postoperatively (OR 0.95, 95% CI 0.92, 0.98), and loss of quadriceps strength between the 2 year and the 10-15 year FU (OR 1.00, 95% CI 1.00, 1.01) showed significantly higher odds for symptomatic radiographic knee OA. Quadriceps muscle weakness after ACL reconstruction was not significantly associated with knee OA.

**Conclusion**

This study detected no association between quadriceps weakness after ACL reconstruction and knee OA as measured 10-15 years later.

Knee injuries, including anterior cruciate ligament (ACL) injuries and meniscal injuries have shown to be some of the most important risk factors for development of knee osteoarthritis (OA).[1,2] However, the causation from the healthy cartilage and bone structures in the knee joint before the injury to the development of knee OA after the injury is still not fully understood. Studies have shown that damage to the cartilage at the time of the injury may initiate disruption of the cartilage matrix, changes in cell metabolism, and also chondrocytes death.[3] The development of knee OA following a knee injury may be influenced by mechanical components such as altered joint loading due to reduced mechanical stability, malalignment, or reduced shock absorption.[3,4] Several risk factors for development of tibiofemoral knee OA have been identified in subjects with ACL injuries, but few studies have examined the association between early impaired knee function and knee OA in long term follow-up studies.[5] Such factors may be important to identify in the early phase after ACL reconstruction to further be able to prevent the onset of knee OA. Meniscal injury and subsequently partial meniscectomy have shown to be important risk factors for knee OA.[6] Quadriceps muscle weakness, which is often seen after ACL injuries,[7] has been shown to increase the knee joint loading patterns with reduced ability to shock absorption, and has thereby been suggested as a significant risk factor for the development of knee OA.[8-11] To our knowledge, no prospective studies with more than 10 years follow-up after ACL reconstruction have investigated quadriceps muscle weakness as a potential risk factor for tibiofemoral OA. Furthermore, prospective long term studies aiming at detecting risk factors for symptomatic radiographic knee OA in subjects with ACL injuries are lacking. The aim of the present study was therefore to identify risk factors associated with radiographic and symptomatic radiographic OA in the tibiofemoral joint 10-15 years after ACL reconstruction. We hypothesized that quadriceps muscle weakness after ACL

reconstruction was a significant risk factor for radiographic and symptomatic radiographic tibiofemoral OA 10-15 years later.

## **MATERIAL AND METHODS**

The present cohort study involved 258 subjects with an ACL rupture. The subjects were consecutively included in the time period between 1990 and 1997 in 4 studies with the same inclusion and exclusion criteria.[12-14] The inclusion criteria were: age between 14 and 50 years; isolated ACL injury or combined with meniscal and/or medial collateral ligament (MCL) injury, and/or chondral lesions, and candidates for ACL reconstruction with bone-patellar-tendon-bone (BPTB) autograft or hamstrings tendon (HT) autograft. Subjects were excluded if they had suffered other major injuries to both the lower extremities less than 1 year before the surgery or if they had suffered ligament injuries in the contralateral knee. All the included subjects went through a supervised rehabilitation program for 6 months postoperatively. The surgical procedures and the rehabilitation programs are described in previous studies.[12-14] The included subjects have been prospectively followed and have been through clinical and functional examinations at 6 months, 1 year, 2 years, and 10-15 years after the ACL reconstruction. The prospective data on clinical and functional outcomes were collected by the same research team and in the same way for all the study participants. On the basis of the similar inclusion and exclusion criteria in the 4 original studies, the materials have been considered to constitute one prospective cohort of subjects.

In the present study subjects with known ACL or meniscal injuries in the contralateral knee suffered during the follow-up period were excluded to use the contralateral knee as a control knee for muscle strength tests, hop tests, and knee joint laxity tests. The additional injuries in the involved knee included MCL injuries (grade I

and II) and chondral lesions identified at the time of the reconstruction, and meniscal injuries suffered at the time of the ACL injury or during the follow-up period. Data of the meniscal injuries, the MCL injuries, and the chondral lesions were collected at the 10-15 year follow-up by reading surgical files of all the included subjects from the index operation and for re-injuries suffered during the follow-up period.

The subjects were informed by written consent before participation at the 10-15 year follow-up evaluation. The study has been evaluated by the Regional Committees for Medical and Health Research Ethics in Eastern Norway.

### **Assessment of knee function**

Knee joint laxity was measured with the KT-1000 knee arthrometer (MEDmetric Corp, San Diego, California) at manual maximum force.[15] The difference in displacement between the two knees was calculated, and expressed in millimeters (mm). The Cincinnati knee score was included to examine self-reported knee function. A score of 100 indicated normal knee function. This self-reported questionnaire has been validated for measuring knee function in ACL injured subjects.[16-18]

Evaluation of muscle strength including knee extension (quadriceps strength) and knee flexion (hamstrings strength) was performed with the Cybex 6000 (Cybex, Division of Lumex, Inc, Ronkonkoma, New York). The isokinetic test protocol consisted of 5 concentric repetitions at 60°/sec. Muscle strength performance was recorded as total work (TW) for all repetitions. The muscle strength values were presented in Joules (J) and J normalized to body weight (%BW) calculated with the formula:  $[(J/BW)*100]$ . Isokinetic muscle strength measurement has been shown to be reliable,[19] and has been widely used in subjects with ACL injury to measure muscle performance.[20]

The triple jump test (recorded in meter) and the stair hop test (recorded in seconds) were included at the 6 month, the 1 year, and the 2 year follow-ups.[21,22] Body mass index (BMI) was measured and calculated with the formula  $\text{kg}/(\text{m}^2)$ .

### **Radiological examination**

Radiological examination was performed only at the 10-15 year follow-up. The SynaFlexer frame (Synarc, Inc, Copenhagen, Denmark) for standardized fixed-flexion positioning (20° knee flexion and 5° external foot rotation) was used for the x-ray procedure. This frame is validated for measurement of joint space width.[23] The pictures were taken bilaterally from a posteroanterior view.

The Kellgren and Lawrence (K&L) classification system[24,25] was used for assessing radiographic changes in the tibiofemoral joint. A K&L score of  $\geq 2$  was used to define radiographic knee OA according to previous literature.[26] Radiographs were read by one radiologist. The clinical and functional results and the type of graft were unknown to the radiologist. Intra-rater reliability test was performed by the radiologist on 35 x-rays (70 knees).

Symptomatic radiographic knee OA was defined on the basis of if the subjects answered positively to a question about if they had experienced knee pain during the last 4 weeks, and in addition had a K&L score of  $\geq 2$ . The question of knee pain was derived from a two-step telephone interview to screen for symptomatic OA developed by Roux et al.[27,28] Knee pain has been shown to be the single symptom that associates most strongly with radiographic OA,[27] and has been included in several studies to define symptomatic radiographic knee OA.[29-31]

## **Statistical analysis**

Statistical Package for Social Sciences (version 16.0, SPSS, Chicago, Illinois) was used for analyzing the data. Means and standard deviations (SD) were presented for descriptive statistics. The Chi square test was used for comparison of categorical variables. The Mann Whitney U test was performed for group comparisons of data that were not normally distributed. Binary logistic regression models with measurement of odds ratio (OR) and 95% confidence intervals (CI) were used to evaluate potential risk factors for radiographic and symptomatic radiographic knee OA. First, univariate analyses were performed for radiographic and symptomatic radiographic knee OA and potential risk factors that included age, gender, additional injury, graft type, time from injury to surgery, BMI, KT-1000 manual maximum tests (difference), and knee function variables at 6 months, 1 year, and 2 years postoperatively (the Cincinnati knee score, the triple jump test, the stair hop test, and the muscle strength tests). The variable “additional injury” constituted meniscal injuries and/or MCL injury, and/or chondral lesion shown at the 10-15 year follow-up, and was dichotomized into “additional injury” or “isolated ACL injury”. Those variables that showed a p-value of  $<0.20$  in the univariate analyses were included in a second analysis with adjustment for age, gender, additional injury, and graft type. The final regression models included variables that were significantly associated with radiographic or symptomatic radiographic knee OA in the second step. A p-value of  $<0.05$  was considered to be statistically significant.

## **RESULTS**

Two hundred and fifty-eight subjects with mean age in the four cohorts of  $27\pm9$  or  $28\pm9$  years were included at the time of ACL reconstruction.[12,32,33] The gender distributions in the four cohorts showed slightly more than 50% males than females



(53-61% vs. 39-47%, respectively). The mean time between injury and surgery was between 27-43±46-64 months in three of the studies, and 9±8 months in one study. About 50% had additional injuries in the four cohorts at the time of ACL reconstruction (range 45-60%).

Two hundred and ten subjects (81%) participated at the 10-15 year follow-up. Of these, 164 had an uninjured contralateral knee and were therefore included in the analyses in the present study (Figure 1). The mean age ( $\pm$ SD) at ACL reconstruction was 27.4±8.7 years, (n=164), the mean time between injury and surgery was 27.2±53.0 months, and the mean time between the ACL reconstruction and the 10-15 year follow-up was 12.1±1.4 years. Subject characteristics are described in Table 1.

Eighty-two subjects (50%) had no additional injuries at the time of the ACL reconstruction. The additional injuries revealed at the time of ACL reconstruction included 36 medial meniscus injuries (22%), 24 lateral meniscus injuries (15%), 7 MCL and meniscus injuries (4%), 13 menisci injuries (8%), and 2 MCL injuries (1%). Twenty-seven subjects (16%) had chondral lesions at the time of the ACL reconstruction. At the 10-15 year follow-up, isolated ACL injury was shown in 70 subjects (43%) and 94 subjects (57%) had additional meniscal and/or MCL injury, and/or chondral lesion. A total of 94 partial meniscectomies were performed in the 88 subjects with additional meniscal injury, either before the ACL reconstruction (18%), during the ACL reconstruction (55%), or during the follow-up period (27%). Furthermore, 9 meniscal tears were sutured before the ACL reconstruction (n=3), at the ACL reconstruction (n=4), or during follow-up (n=2).

Radiographic knee OA (K&L  $\geq$  2) was detected in 113 subjects (69%) (Table 2). Of the 77 subjects that reported knee pain at the 10-15 year follow-up, 58 subjects (75%) had K&L  $\geq$  grade 2 and 19 subjects (25%) had no radiographic changes (Table 2).

### **Risk factors for knee OA**

Quadriceps weakness measured after the ACL reconstruction both in absolute values (J) or absolute values normalized to BW (%BW) was not significantly associated with radiographic or symptomatic radiographic knee OA identified 10-15 years later (Table 3 and 4). Furthermore, no other functional test results were significantly associated with radiographic knee OA (Table 3).

Low Cincinnati knee score at the 2 year follow-up and loss of quadriceps strength between 2 to 10-15 years were significantly associated with symptomatic radiographic knee OA adjusted for age, gender, additional injury, and graft type (Table 4).

The final regression models for the risk factor analyses included variables that were significantly associated with radiographic or symptomatic radiographic knee OA adjusted for age, gender, additional injury, and graft type (Table 5). Subjects with increased age at surgery (OR 1.06, 95% CI 1.01, 1.11) and additional injury (OR 2.05, 95% CI 1.00, 4.20) had significantly higher odds for radiographic knee OA. Furthermore, subjects with impaired self-reported knee function at 2 years postoperatively had significantly higher odds for symptomatic radiographic knee OA (OR 0.95, 95% CI 0.92, 0.98). The odds for symptomatic radiographic knee OA increased with 5% for each unit decrease in the Cincinnati knee score at 2 years after the ACL reconstruction. Also loss of quadriceps strength between 2 to 10-15 years showed significantly higher odds for symptomatic radiographic knee OA (OR 1.00, 95% CI 1.00, 1.01). Males tended to have higher odds for symptomatic radiographic knee OA compared to females (OR 2.19, 95% CI 1.00, 4.80).

## DISCUSSION

Previous studies have highlighted that quadriceps weakness may be a risk factor for development of knee OA.[8,9,34] Our hypothesis that quadriceps weakness after ACL reconstruction was a risk factor for knee OA 10-15 years later was not confirmed. Risk factors associated with radiographic knee OA were increased age at the time of surgery and meniscal injury and/or chondral lesion. Furthermore, factors that associated with symptomatic radiographic knee OA included self-reported knee function at 2 years postoperatively, and loss of quadriceps strength between the 2 year and the 10-15 year follow-up.

To our knowledge, this is the first prospective long term follow-up study evaluating quadriceps weakness as a risk factor for knee OA in subjects who have undergone ACL reconstruction. However, a few population-based studies have evaluated the association between quadriceps weakness and knee OA: Slemenda et al.[9] suggested that quadriceps weakness was a risk factor for radiographic knee OA in women, but not in men, in a study of elderly with no known knee injuries. They found that subjects who developed knee OA 30 months later were 18% weaker at baseline than those who did not develop knee OA ( $p=0.053$ ). Our results revealed no significant differences in quadriceps strength values between those with radiographic knee OA compared to those without radiographic knee OA either at 6 months (0%), 1 year (3%), or 2 years (5%) postoperatively. However, our cohort consisted of younger individuals with previous knee injuries, and the subjects in our study had gone through a rehabilitation program aiming at retaining muscle strength after the ACL reconstruction. Thus, a comparison between the two studies cannot be performed. The study by Slemenda et al.[9] is widely cited for supporting that quadriceps weakness relative to body weight is a risk factor for development of radiographic knee OA, but few studies

have reproduced similar results.[34,35] Nevertheless, their cohort of subjects *with* knee OA after 31 months of follow-up consisted of only 13 subjects in whom 7 had unilateral knee OA at baseline. In addition, the analyses did not include adjustment for potential confounding factors such as age or knee injuries suffered during the follow-up period. Segal et al.[36] studied the effect of thigh muscle strength on knee OA in subjects between 50-79 years (mean 62±8). They could not document that quadriceps weakness was a risk factor for radiographic knee OA 30 months later. However, they concluded that quadriceps weakness seemed to predict symptomatic radiographic knee OA. Their cohort included subjects with known risk factors for knee OA, such as obesity or prior knee injuries. Currently, there is no evidence showing that quadriceps weakness as a single factor is a risk factor for development of knee OA in subjects with ACL injury. Based on recent studies [35,36] and our study, quadriceps muscle weakness did not seem to be a risk factor for radiographic knee OA in different populations. Nevertheless, our results showed that subjects who lost quadriceps strength between 2 years and 10-15 years after the ACL reconstruction had higher odds for symptomatic radiographic knee OA. Because we had no radiographic data before the 10-15 year follow-up, we do not know what occurred first, the quadriceps weakness or the symptomatic radiographic knee OA. However, quadriceps weakness has been shown to correlate with knee pain,[37] thus, the association between loss of quadriceps strength between 2 years and 10-15 years after the ACL reconstruction and symptomatic radiographic OA may be an association with the knee pain only. The fact that quadriceps weakness at 6 months, 1 year, and 2 years after ACL reconstruction was not associated with symptomatic radiographic OA may indicate that the loss of quadriceps strength during the long term follow-up have been a consequence of the knee pain. Pain inhibition and thereby activation failure has been shown to reduce muscle function in subjects with

knee OA.[4] Therefore, the loss of quadriceps strength for subjects with symptomatic radiographic knee OA seen in our cohort may be due to inhibition triggered by pain. Abnormal muscle function influences the magnitude of the knee joint loading, and abnormal loading patterns during walking has been associated with the onset of knee OA.[4] Normal muscle function, including muscle strength, activation patterns, and proprioceptive acuity, is a key factor to sustain the activity level and to reduce pain in all age groups. [38] Thus, to restore normal muscle function should be one of the main aims after ACL reconstruction.

Several risk factors have been associated with knee OA in subjects with previous ACL injury such as meniscal injury, BPTB graft, chondral lesions, loss of knee extension, increased knee joint laxity, increased time between the injury and the surgery, and increased age at injury.[6] Other factors that have been associated with knee OA include obesity, <90% performance on single leg hop test compared to the uninjured side 1 year after surgery, high level of sports activity, OA of the contralateral knee, and time duration of follow-up.[5,11,39,40] Our results supported that meniscal injury alone or combined with chondral lesion, and increased age were associated with radiographic knee OA also in line with a newly published study by Keays et al.[11] In the present study, most of the subjects with chondral lesions also had meniscal injuries, therefore, chondral lesions could not be studied as a separate risk factor. However, strong evidence exists that meniscal injuries and subsequently partial meniscal resections are risk factors for development of knee OA following an ACL injury.[6] Also subjects with isolated meniscal injury have shown high prevalence of knee OA.[2] The menisci functions as shock absorbers and transmit load in the knee joint during movement and static loading.[41] Removal of parts of one or both the menisci leads to altered loading on the cartilage, and consequently may initiate the onset of OA. More effort should

therefore be put on prevention of meniscal injuries, but also treatment strategies including less resection procedures in order to sustain the role of the menisci after the injury. In our study, more than 95% of those with meniscal injuries were partially meniscectomized. Consequently, we were not able to evaluate the association between type of meniscal treatment and knee OA.

The results in the present study revealed differences in the risk factors reported for subjects with previous knee injuries compared to older subjects with knee OA. For instance, obesity has been reported to be an important risk factors for knee OA.[42] However, our cohort showed low mean BMI and may thus not be comparable to population-based studies. Furthermore, females have shown to have higher prevalence of knee OA than males, but in the present study, the males tended to show higher odds for symptomatic radiographic knee OA compared to the females. We have no good explanation for this difference, but the higher prevalence of knee OA seen for males may be due to unknown confounders such as malalignment, knee demanding occupations, or higher activity level. But no differences were detected between the females and the males on the Tegner activity scale at the 10-15 year follow-up. BPTB graft has been significantly associated with radiographic knee OA in subjects with ACL reconstruction.[5,11] Our analysis detected a trend towards higher odds for radiographic knee OA for subjects with BPTB graft compared to those with HT graft ( $p=0.07$ ). Nevertheless, few subjects with HT graft were included in the study which may have influenced the results.

The subjects with impaired self-reported knee function 2 years after ACL reconstruction had higher odds for symptomatic radiographic knee OA. Thus, those with impaired knee function 2 years postoperatively seemed to be at risk for symptomatic radiographic knee OA. No radiological assessment was included at the 2 year follow-up,

therefore, it is difficult to state the onset of the radiographic changes in the tibiofemoral joint. Even though 16% had chondral lesions at the time of injury, it is reasonable to believe that few subjects had radiographic knee OA 2 years postoperatively in subjects with mean age of  $27.4 \pm 8.7$  years.[43]

This prospective study is the first to provide important knowledge on the association between quadriceps muscle weakness and knee OA in subjects with ACL reconstruction. However, the study did not include radiographic evaluation at all the follow-ups, resulting in lack of information on the onset of radiographic knee OA. Therefore, no conclusion on causality between quadriceps muscle weakness and knee OA can be drawn. Furthermore, our results on the association between quadriceps weakness and knee OA can not be generalized to subjects in the same age group without knee injuries. The study cohort revealed a high prevalence of mild radiographic knee OA and few subjects had severe radiographic knee OA. This may have influenced the results. Our study included several potential risk factors, but our study did not include data on activity level, malalignment, bone mineral density, biochemical markers, nutritional factors, or socioeconomic factors which have previously been associated with knee OA.[44,45] Finally, a definition of symptomatic radiographic knee OA according to one question on knee pain during the last 4 weeks additionally to radiographic signs may have overestimated the amount of subjects with symptomatic radiographic knee OA because the knee pain could be caused by other factors unrelated to OA. Contrarily, subjects with radiographic knee OA may have been misclassified to not having symptomatic radiographic OA if the subjects had no pain during the last 4 weeks.

## **CONCLUSION**

Increased age at the time of ACL reconstruction and meniscal injury and/or chondral lesion were significant risk factors for radiographic knee OA. Subjects with impaired knee function at 2 years after ACL reconstruction had significantly higher odds for symptomatic radiographic knee 10 years later. Quadriceps muscle weakness after ACL reconstruction was not a risk factor for radiographic or symptomatic radiographic knee OA at 10-15 years after ACL reconstruction.

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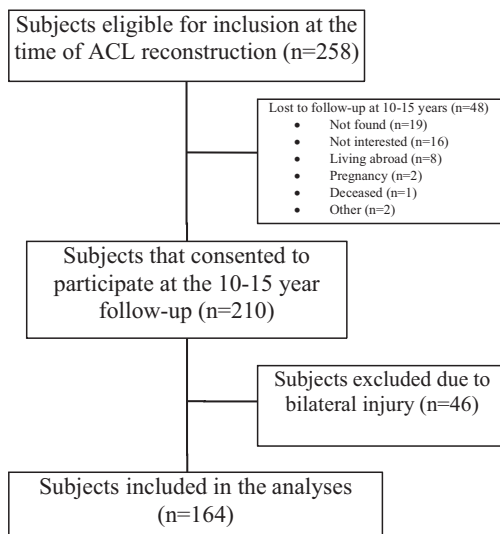


Figure 1. Flow chart of the study participants

Table 1. Patients characteristics (n=164)

| <b>Variable</b>  |                              | <b>Frequency</b> | <b>%</b> |
|--|------------------------------|------------------|----------|
| Gender   | Male                         | 93               | 57       |
|  | Female                       | 71               | 43       |
| Graft type   | HT                           | 22               | 13       |
|  | BPTB                         | 142              | 87       |
| Activities performed at the time of the ACL injury                   | Ball activities              | 96               | 58       |
|  | Alpine                       | 36               | 22       |
|  | Other                        | 20               | 12       |
|  | Missing                      | 13               | 8        |
| Additional injuries at the 10-15 year follow-up in the involved knee | Isolated injury              | 70               | 43       |
|  | Medial meniscus              | 28               | 17       |
|  | Lateral meniscus             | 17               | 11       |
|  | Meniscii                     | 18               | 11       |
|  | Meniscus and MCL             | 4                | 1        |
|  | Meniscus and chondral lesion | 21               | 13       |
| Chondral lesion  |                              | 6                | 4        |

HT, hamstrings tendon; BPTB, bone-patella-tendon-bone; MCL, medial collateral ligament.

Table 2. Frequencies (%) of the Kellgren and Lawrence (K&L) scores and knee pain (n=164)

| <b>K&amp;L score</b> | <b>Injured knee</b> | <b>Uninjured knee</b> | <b>Knee pain (n=77)</b> |
|----------------------|---------------------|-----------------------|-------------------------|
| Grade 0              | 17 (10)             | 106 (65)              | 7 (9)                   |
| Grade 1              | 34 (21)             | 34 (21)               | 12 (16)                 |
| Grade 2              | 72 (44)             | 20 (12)               | 38 (49)                 |
| Grade 3              | 32 (19)             | 4 (2)                 | 14 (18)                 |
| Grade 4              | 9 (6)               | 0 (0)                 | 6 (8)                   |

Table 3. Binary logistic regression analyses of the association between radiographic knee OA and potential risk factors

| Variables   | Crude<br>OR (95% CI) | p-value | Adjusted<br>OR (95% CI) | p-<br>value |
|---|----------------------|---------|-------------------------|-------------|
| Age   | 1.07 (1.03, 1.12)    | 0.002   |                         |             |
| Gender*   | 2.23 (1.14, 4.37)    | 0.020   |                         |             |
| Additional injury*  | 2.6 (1.32, 5.14)     | 0.006   |                         |             |
| Graft type*   | 2.25 (1.02, 6.35)    | 0.044   |                         |             |
| Time from injury to surgery                                       | 1.00 (0.99, 1.01)    | 0.758   |                         |             |
| Body mass index   |                      |         |                         |             |
| 6 months  | 1.08 (0.97, 1.20)    | 0.144   | 1.04 (0.93, 1.17)       | 0.487       |
| 1 year  | 1.18 (1.02, 1.36)    | 0.027   | 1.04 (0.87, 1.24)       | 0.647       |
| 2 years   | 1.15 (1.00, 1.32)    | 0.051   | 1.00 (0.85, 1.19)       | 0.925       |
| KT-1000, difference, mm   |                      |         |                         |             |
| 6 months  | 0.99 (0.87, 1.12)    | 0.882   |                         |             |
| 1 year  | 1.02 (0.88, 1.16)    | 0.812   |                         |             |
| 2 years   | 0.96 (0.84, 1.10)    | 0.568   |                         |             |
| Cincinnati knee score   |                      |         |                         |             |
| 6 months  | 0.99 (0.96, 1.01)    | 0.330   |                         |             |
| 1 year  | 0.99 (0.96, 1.02)    | 0.405   |                         |             |
| 2 years   | 0.99 (0.96, 1.02)    | 0.548   |                         |             |
| Triple jump test, meter   |                      |         |                         |             |
| 6 months  | 1.00 (0.99, 1.00)    | 0.971   |                         |             |
| 1 year  | 1.00 (0.99, 1.00)    | 0.211   |                         |             |
| 2 years   | 1.00 (0.99, 1.00)    | 0.367   |                         |             |
| Stair hop test, seconds   |                      |         |                         |             |
| 6 months  | 0.99 (0.96, 1.03)    | 0.850   |                         |             |
| 1 year  | 0.98 (0.94, 1.03)    | 0.590   |                         |             |
| 2 years   | 0.98 (0.93, 1.04)    | 0.490   |                         |             |
| Hamstrings strength (J)   |                      |         |                         |             |
| 6 months  | 1.00 (0.99, 1.00)    | 0.999   |                         |             |
| 1 year  | 1.00 (0.99, 1.00)    | 0.236   |                         |             |
| 2 years   | 1.00 (1.00, 1.00)    | 0.075   | 1.00 (0.99, 1.00)       | 0.726       |
| Quadriceps strength (J)   |                      |         |                         |             |
| 6 months  | 1.00 (0.99, 1.00)    | 0.803   |                         |             |
| 1 year  | 1.00 (0.99, 1.00)    | 0.632   |                         |             |
| 2 years   | 1.00 (0.99, 1.00)    | 0.230   |                         |             |
| Quadriceps strength (%BW)   |                      |         |                         |             |
| 6 months  | 0.99 (0.99, 1.00)    | 0.206   |                         |             |
| 1 year  | 0.99 (0.99, 1.00)    | 0.233   |                         |             |
| 2 years   | 1.00 (0.99, 1.00)    | 0.969   |                         |             |
| Quadriceps strength ≤80% versus >80% of uninjured knee, 6 months* | 1.07 (0.48, 2.36)    | 0.874   |                         |             |
| Increased quadriceps strength 6 months-2 years (J)                | 0.99 (0.99, 1.00)    | 0.073   | 1.00 (0.99, 1.00)       | 0.548       |
| Decreased quadriceps strength 2 -10-15 years (J)                  | 1.00 (0.99, 1.00)    | 0.282   |                         |             |

OA, osteoarthritis; OR, odds ratio; CI, confidence interval; J, Joule; BW, body weight. Adjusted for age, gender, additional injury, and graft type; Dependent variable: K&L  $\geq 2$  (OA: n=113, no OA: n=51); \*Reference categories are females, isolated **ACL** injury, hamstrings tendon graft, and quadriceps strength <80%; The strength tests and the hop tests are given for the injured leg.



Table 4. Binary logistic regression analyses of the association between symptomatic radiographic knee OA and potential risk factors

| Variables   | Crude<br>OR (95% CI) | p-value | Adjusted<br>OR (95% CI) | p-<br>value |
|---|----------------------|---------|-------------------------|-------------|
| Age   | 1.01 (0.97,1.05)     | 0.461   |                         |             |
| Gender*   | 1.76 (0.9, 3.4)      | 0.094   |                         |             |
| Additional injury*  | 1.9, (0.98, 3.7)     | 0.059   |                         |             |
| Graft type*   | 2.7 (0.9, 8.6)       | 0.079   |                         |             |
| Time from injury to surgery   | 1.0 (0.99, 1.01)     | 0.958   |                         |             |
| BMI   |                      |         |                         |             |
| 6 months  | 0.99 (0.89, 1.09)    | 0.805   |                         |             |
| 1 year  | 1.07 (0.94, 1.22)    | 0.296   |                         |             |
| 2 years   | 1.03 (0.91, 1.18)    | 0.556   |                         |             |
| KT-1000, difference, mm   |                      |         |                         |             |
| 6 months  | 0.97 (0.86, 1.09)    | 0.577   |                         |             |
| 1 year  | 0.96 (0.84, 1.10)    | 0.560   |                         |             |
| 2 years   | 0.94 (0.82, 1.07)    | 0.330   |                         |             |
| Cincinnati knee score   |                      |         |                         |             |
| 6 months  | 0.98 (0.95, 1.00)    | 0.077   | 0.97 (0.95, 1.00)       | 0.059       |
| 1 year  | 0.97 (0.94, 0.99)    | 0.041   | 0.97 (0.95, 1.00)       | 0.080       |
| 2 years   | 0.95 (0.93, 0.98)    | 0.001   | 0.95 (0.92, 0.98)       | 0.001       |
| Triple jump test, meter   |                      |         |                         |             |
| 6 months  | 1.00 (0.99, 1.00)    | 0.500   |                         |             |
| 1 year  | 1.00 (0.99, 1.00)    | 0.203   |                         |             |
| 2 years   | 1.00 (0.99, 1.00)    | 0.320   |                         |             |
| Stair hop test, meter   |                      |         |                         |             |
| 6 months  | 0.99 (0.96, 1.03)    | 0.760   |                         |             |
| 1 year  | 1.00 (0.96, 1.05)    | 0.970   |                         |             |
| 2 years   | 1.00 (0.95, 1.06)    | 0.840   |                         |             |
| Hamstrings strength (J)   |                      |         |                         |             |
| 6 months  | 1.00 (0.99, 1.00)    | 0.696   |                         |             |
| 1 year  | 1.00 (0.99, 1.00)    | 0.428   |                         |             |
| 2 years   | 1.00 (0.99, 1.00)    | 0.288   |                         |             |
| Quadriceps strength (J)   |                      |         |                         |             |
| 6 months  | 1.00 (0.99, 1.00)    | 0.981   |                         |             |
| 1 year  | 1.00 (0.99, 1.00)    | 0.596   |                         |             |
| 2 years   | 1.00 (0.99, 1.00)    | 0.297   |                         |             |
| Quadriceps strength (%BW)   |                      |         |                         |             |
| 6 months  | 1.00 (0.99, 1.00)    | 0.955   |                         |             |
| 1 year  | 1.00 (0.99, 1.00)    | 0.935   |                         |             |
| 2 years   | 1.00 (0.99, 1.00)    | 0.672   |                         |             |
| Quadriceps strength ≤80%<br>versus >80% of uninjured<br>knee, 6 months* | 0.86 (0.41, 1.80)    | 0.698   |                         |             |
| Increased quadriceps strength<br>6 months-2 years (J)                   | 0.99 (0.99, 1.00)    | 0.346   |                         |             |
| Decreased quadriceps<br>strength 2 years-10-15 years<br>(J)             | 1.00 (1.00, 1.00)    | 0.029   | 1.00 (1.00, 1.00)       | 0.046       |

OA, osteoarthritis; OR, odds ratio; CI, confidence interval; Joule, J; BW, body weight; Adjusted for gender, age, additional injury, and graft type; Dependent variable: Symptomatic radiographic OA (OA: n=58, no OA: n=106); \*Reference categories are females, isolated ACL injury, hamstrings tendon graft, and quadriceps strength <80%. The strength results and the hop tests are given for the injured leg.

Table 5. The final logistic regression models including potential risk factors for radiographic OA (n=164) and symptomatic radiographic OA (n=141) in subjects with ACL reconstruction

| <b>Dependent variable</b>             | <b>Potential risk factors</b>                        | <b>Number</b> | <b>OR</b> | <b>95% CI</b> | <b>p-value</b> |
|---------------------------------------|--|---------------|-----------|---------------|----------------|
| Radiographic OA<br>(n=113)            | Age at surgery                                       | 164           | 1.06      | 1.01, 1.11    | 0.014          |
|                                       | Additional injury                                    |               |           |               |                |
|                                       | No   | 70            | 1.00      |               |                |
|                                       | Yes  | 94            | 2.05      | 1.00, 4.20    | 0.049          |
|                                       | Gender   |               |           |               |                |
|                                       | Females  | 71            | 1.00      |               |                |
| Symptomatic radiographic OA<br>(n=50) | Males  | 93            | 1.72      | 0.84, 3.54    | 0.138          |
|                                       | Graft type   |               |           |               |                |
|                                       | Hamstrings   | 22            | 1.00      |               |                |
|                                       | Patellar   | 142           | 2.49      | 0.93, 6.67    | 0.070          |
|                                       | Cincinnati at 2 years                                | 141           | 0.95      | 0.92, 0.98    | 0.003          |
|                                       | Loss of quadriceps strength,<br>2 to 10-15 years (J) |               |           |               |                |
| Symptomatic radiographic OA<br>(n=50) | Gender   |               |           |               |                |
|                                       | Females  | 141           | 1.00      | 1.00, 1.01    | 0.037          |
|                                       | Males  | 62            | 1.00      |               |                |
|                                       | Additional injury                                    |               |           |               |                |
|                                       | No   | 79            | 2.19      | 1.00, 4.80    | 0.050          |
|                                       | Yes  | 58            | 1.00      |               |                |
| Graft type                            | Hamstrings   | 83            | 1.51      | 0.68, 3.33    | 0.306          |
|                                       | Patellar   | 20            | 1.00      |               |                |
|                                       |  | 121           | 2.39      | 0.69, 8.25    | 0.168          |

OA, osteoarthritis; ACL, anterior cruciate ligament; OR, odds ratio; CI, confidence interval; J, Joule.

